ATLAS OF CLINICAL HEMATOLOGY

By

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To

HAL DOWNEY, PH D

(1877—1959)

Late Professor Emeritus of Anatomy
University of Minnesota

This volume is respectfully and affectionately dedicated by the author

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PREFACE

Hematology as we know it now began to evolve over a century ago as a scion as it were of pathocytology and as such it has drawn heavily on the resources of its progenitors in attaining the maturity which we see today However since Ehrlich discovered more or less specific stains for blood cells the systematic study of blood has gradually come to assume an independent position in the comity of natural sciences Although there is no complete uniformity of opinion in regard to the interpretation of pathologic changes the experiences and observations of many investigators have furnished an empirical means of evolving a morphologic classification of blood diseases by which the clinician establishes his diagnosis and proceeds with therapeutic management Having been assigned to the care of patients with blood disorders who came to the Bobs Roberts Hospital of the University of Chicago the author began to collect all blood smears made from these patients and to make drawings of some of these for educational purposes These drawings together with those made from the smears kindly loaned by others were shown as a Scientific Exhibit at the annual convention of the American Medical Association held in San Francisco in 1938 They were later published in 2 volumes (1954 and 1958) in Japan in the form of an atlas of clinical hematology The author wishes to express his grateful appreciation for the encouragement shown him by Dr Henry M Stratton of Grune & Stratton Inc in undertaking the publication of its English edition

Katsuji Kato

Tokyo Japan
January 1 1960

EXPLANATORY REMARKS

1 The plates reproduced in original colors have been selected from a collection of drawings made by the author himself during a period of about 25 years The smear preparations from which these drawings were made had been obtained mostly from the patients personally observed but a certain number of them were kindly loaned by various authors who published their cases in the literature

2 The drawings were made under uniform conditions as much as the circumstances permitted including

(a) Routine staining of smears using modified Romanowsky s method

(b) Uniform magnification (approximately 1300 × in the original) by the use of a camera lucida

(c) Reduction to about 1000 × magnification for engraving

Under these specifications the cells reproduced may be readily compared with each other and the cell diameter may be estimated conveniently by means of a millimeter rule 1 mm being equivalent to about 1 micron

3 Each plate is printed on the right side of the page with an outline drawing of the cells reproduced on the opposite left side thus immediately facing the color plate A short legend accompanies the line drawing and the important cells are indicated by appropriate abbreviations of their names A brief introductory description of the disease with a list of selected references precedes each plate or a group of related plates

4 The cells shown on each plate were selected for drawing from the entire smear for the sole purpose of emphasizing and reiterating the morphologic characteristics and therefore no plate represents a photographic picture of any one microscopic field

I MONOPHYLETIC THEORY OF HEMOCYTOGENESIS

The origin development and interrelationships of the formed elements of the blood have been repeatedly discussed by both anatomists and pathologists but the subject is so full of controversies that the average clinician often finds it difficult to decide just which theory is the most suitable one to follow for routine work The monophyletic view previously published by the author in 1935 is here reviewed with slight modifications in the nomenclature in the hope that it may be useful in interpreting the blood pictures reproduced in this Atlas

Broadly speaking all schools of hematologic thought may be classified under either monophyletism (unitarianism neo unitarianism extreme unitarianism) or polyphyletism (dualism trialism complete polyphyletism) The grounds on which all of these theories are based are undoubtedly and indisputably sound even though there may be some differences in the interpretation of various cells in respect to their interrelationships

The monophyletic scheme here proposed (Plate 1) comprises five concentric zones (numbered centrifugally by Arabic numerals 1 to 5) representing the sequence of cell maturation The radiating lines which cross Zones 3 4 and 5 divide the blood cells into nine distinct and specific groups (numbered clockwise by Roman numerals I to IX) The fact that these radiating lines do not traverse the first and second zones implies that the cells in these two zones maintain general or common relationships to all of the specific cell groups It is this particular feature which distinguishes the monophyletic from polyphyletic schools

The precursor of all blood cells is the undifferentiated mesenchymal cell of the embryo (Zone 1) corresponding in the adult organism to the resting reticuloendothelial cell a fixed tissue cell which is not a hemocyte This cell often referred to as the reticulum cell is endowed with almost unlimited developmental potentialities capable of differentiating into the free stem cell of the blood (hemocytoblasts of Ferrata myeloblasts of Downey) or into any functioning cell (macrophage of Metchnikoff polyblast of Maximow) according to environmental demands In the blood forming organs the earliest general hemoblast developing from this precursor functions as a common parent to all of the nine specific cell groups This stem cell is depicted in Zone 2 where all of the five cells shown are morphologically identical each being characterized by a peculiarly homogeneous pattern of nuclear chromatin and provided with a scanty amount of basophilic cytoplasm The deeply stained chromatin granules of the relatively large nucleus are delicately fine or leptochromatic showing no tendency to form aggregations The nucleoli varying in both number and size are distinctly visible The cytoplasm represented by a narrow rim around the nucleus takes on a muddy blue tint Immediately surrounding the nucleus there may be seen a narrow slightly creamy hyaline clear area The nuclear membrane is as a rule very indistinct

In the literature this general stem cell is somewhat synonymously called lymphoidocyte (Pappenheim) hemocytoblast (Ferrata) myeloblast (Downey) or the indifferent lymphoid cell of the marrow (Michaelis and Wolff) Maximow however was unable to distinguish his lymphocyte from this cell on the basis of cytologic characteristics and his hemocytoblast is not the same cell here being

described The myeloblast of Naegeli appears to comprise the cell of this type as well as the one containing a few azurophilic granules in the cytoplasm The term hemocytoblast with Ferrata s connotation seems to be most suitable and appropriate

Sectors I and II illustrate the cells of the erythrocytic series of which the primitive (fetal) and the definitive (adult) types can be distinguished For the purpose of description the former will be referred to as the megaloblastic while the latter as the normoblastic series In the megaloblastic group the earliest form is the promegaloblasts (Sector I Zone 3) otherwise known as embryonic rubriblast or erythrogone characterized by somewhat coarsely granular chromatin of the nucleus and intensely basophilic cytoplasm containing no trace of hemo globin The parachromatin spaces are often clearly discernible but nuclear membrane is usually indistinct There may be a few visible nucleoli This cell develops into the megaloblast (Sector I Zone 4) which may be either poly chromatophilic or orthochromatic according to the amount of fetal hemoglobin synthesized in the cytoplasm The most distinctive feature of this cell consists in the advanced degree of hemoglobin fabrication which is far ahead of the extent of *nuclear chromatin condensation However the cytoplasm* often contains a few blue staining granules The most mature cell of the megaloblastic group is the megalocyte (Sector I Zone 5) sometimes called macrocyte resulting from complete extrusion of the nuclear remains

In the normoblastic series the pronormoblast (Sector II Zone 3) is the most primitive form otherwise referred to as prorubricyte or proerythroblast This hemocyte is characterized by the nuclear chromatin granules forming coarse aggregations presenting a suggestion of cart wheel arrangement thus rendering the nucleoli to be difficult of recognition The cytoplasm either homogeneous or finely granular is deeply basophilic and often assumes an irregular contour The presence of hemoglobin in the cytoplasm is not yet detectable but in the early normoblast (Sector II Zone 4) or rubricyte the cytoplasm becomes definitely polychromatophilic indicating the beginning of adult hemoglobin synthesis The nuclear chromatin has become condensed to such an extent that the nucleoli are no longer identifiable and a typical cart wheel pattern can be recognized In the late normoblast or metarubricyte the nucleus is represented by a dark stained mass and the cytoplasm has become completely orthochromatic When the pyknotic nuclear mass assumes a dot like appearance it is known as *Howell-Jolly body The polychromatic erythrocytes are the reticulocytes* in which the fine granular network (substantia granulofilamentosa) can be demonstrated by means of supravital staining The completely mature orthochromatic red cell containing neither the supravitally stainable metachromatic granular structure nor any nuclear remains is the normal erythrocyte or normocyte (Sector II Zone 5)

The development and maturation of the megakaryocyte and thrombocyte are traced in Sector III of which the most immature form is the megakaryoblast (Zone 3) *Surrounded by a definitely hyaline zone and containing distinctly* visible nucleoli the nucleus of this hemocyte is marked by a somewhat densely packed reticular chromatin arrangement The cytoplasm stains slate gray but it may also be muddy blue at the periphery shading into the creamy hyaline area as it approaches the nucleus This cell which is by far the largest of all bone marrow elements develops into the promegakaryocyte (Zone 4) the cytoplasm

of which increases in volume to enormous dimensions while the nucleus assumes a typically multilobulated configuration Some azurophilic granules begin to appear in the hyaline ground substance of the cytoplasm and these granules (dusts) take on a reddish purple color but the oxidase or peroxidase reaction is entirely negative The final stage of maturation is reached when the typical megakaryocyte (Zone 5) develops a fully ripened cytoplasm packed with azuro philic granules and finally presenting an extremely irregular and ragged contour Portions of the cytoplasm may be seen breaking off as individual platelets or thrombocytes which are then shed into the circulating blood Occasionally however even small nuclear fragments may find their way into the peripheral blood

The thrombocytes or blood platelets are thus essentially small torn-off masses of megakaryocytic cytoplasm normally measuring from 2 to 4 microns in diameter although in certain diseases a few giant platelets may be found in the blood The typical thrombocyte is made up of two distinct parts namely the chromomere or granulomere containing highly refractile reddish purple granules and the hyalomere consisting of homogeneous substance and exhibiting a flexible mucinous character The thrombocytes are concerned primarily in blood coagulation because of their inherent properties to interact with certain plasmatic constituents particularly fibrinogen Under pathologic conditions the thrombocytes may be greatly reduced in number as in idiopathic and toxic thrombocytopenic states or markedly increased as in idiopathic throm bocythemia and postoperative thrombocytosis

Sectors IV V and VI illustrate the three well known varieties of specific granulocytes of which the myeloblast (in the narrow sense) is the common parent to all of these meyloid cells The three hemocytes depicted in Zone 3 are of this type perhaps corresponding to the leukoblasts of Pappenheim and contain in the cytoplasm a limited number of granules either azurophilic or specific

The maturation of the eosinophilocyte is traced in Sector IV the youngest form being the eosinophilic myelocyte (Zone 4) which after passing through the metamyelocyte stage (Zone 5 A) develops into the typical eosinophilocyte (Zone 5 B) The nucleus of the mature cell is usually segmented into two lobes but occasionally presents a multilobulated configuration The cytoplasm is pale blue in ground substance and normally contains tightly packed specifically red stained granules which are spherical in shape and relatively uniform in size When fully matured these granules are intensely acidophilic but in the im mature stage they may be stained dark gray in color

The developmental sequence of neutrophilic granulocytes is shown in Sector V of which the promyelocyte or premyelocyte (Zone 4 A) is generally the largest in size The cytoplasm is characterized by the evolution of neutrophilic granules in adition to nonspecific azurophilic granules which may be quite abundant while still containing some basophilic substance of its precursor The nucleus is yet immature but the chromatin substance begins to show early clumping In the myelocyte (Zone 4 B) the specific granules have fully matured and completely fill the cytoplasmic area The pattern of nuclear chromatin suggests complete maturity but the nucleus itself is still immature in that the shape is either round or oval The three stages of more mature neutrophilocytes are called respectively the metamyelocyte (Zone 5 A) staff cell or rhabdocyte (Zone 5 B)

and polymorphonuclear form or segmentocyte (Zone 5 C) As the granulocytes mature the number of nuclear segments or lobules increase each being connected with its neighbor by means of a thin filament The hemograms devised by Arneth Schilling or others and frequently utilized in clinical diagnosis are constructed on the basis of nuclear segmentation In pernicious anemia there may appear a certain number of giant neutrophils provided with multisegmented nuclei known as macropolycytes of Cooke which are often regarded as one of the diagnostic criteria of this disease These cells are found in the peripheral blood but are particularly abundant in the bone marrow and distinguished from the hypersegmented polycytes of unusually large size occurring in acute or chronic infection

The basophilic myelocyte (Sector VI Zone 4) possesses a rather grayish blue cytoplasm containing a few specific granules and a round or oval nucleus provided with clumped chromatin threads The structure of the basophilic metamyelocyte (Zone 5 A) is characterized by a tendency of the nucleus to divide into segments as indicated by the indentation formed on one side and by the development of an increasing number of specific granules In the mature basophilocyte (Zone 5 B) the nucleus which is composed of rather ill defined segments, occupies a relatively large area and the basophilic granules of irregular and uneven size are abundantly distributed throughout the entire cell The question as to whether or not the basophilic leukocytes of the blood and bone marrow are identical with the mast cells of the tissue appears to be as yet not entirely settled

Sector VII contains the hemocytes of the monocytic series of which the primitive form is the monoblast (Zone 3) This youngest cell is characterized by its large size a tendency of the nuclear chromatin to assume a finely reticular arrangement and the presence of clearly recognizable nucleoli The cytoplasm presents a distinctly granular appearance and stains moderately deep blue This form matures into the promonocyte (Zone 4) still relatively large in size the nucleus of which begins to show a tendency to become indented on one side The cytoplasm in addition to being granular contains a fair amount of azurophilic granules usually congregated near the nuclear indentation The mature monocyte (Zone 5) is characterized by the presence of abundantly developed azurophilic granules distributed diffusely throughout the cytoplasm The nuclear pattern is notably reticular in chromatin arrangement and the shape of the nucleus may vary from either round or oval to highly irregular globe shaped configurations

The cells of the lymphatic series are shown in Sector VIII the most primitive form being the lymphoblast (*Zone 3*) which develops from the hemocytoblast *in the lymphoid tissue or lymphogone* This cell is characterized by a fair amount of basophilic cytoplasm and a somewhat coarse chromatin pattern of the nucleus The nucleoli usually two in number are distinctly visible The next stage of maturation is represented by the prolympnocyte (Zone 4 A and B) either large or small in size with a nucleus composed of definitely aggregated chromatin strands Usually there is only a single nucleolus which can be clearly recognized The cytoplasm appears peculiarly hyaline and transparent taking on a sky blue tint and showing no tendency to become granular The fully mature lymphocyte may be large medium or small so classified solely on the basis of the over all dimensions of the cell The large lymphocyte (Zone 5 A)

has a nucleus with characteristically heavy and clumped chromatin while its cytoplasm presents an entirely homogeneous appearance Occupying the intermediate position is the medium lymphocyte or mesolymphocyte (Zone 5 B) which occasionally reveals a few metachromatic granules in the cytoplasm The small lymphocyte (Zone 5 C) has a very small amount of deeply basophilic cytoplasm and a nucleus with heavily condensed chromatin masses The developmental potencies of the lymphocyte have been pointed out from time to time especially by the extreme unitarians who believe that under certain conditions of abnormal stimulation this hemocyte may undergo dedifferentiation back to the hemocytoblast stage which may then redifferentiate into any type of blood cells

The hemocytes commonly called plasma cells or plasmacytes are grouped together in Sector IX and arranged according to the sequence of their presumable maturation order The usual and most mature form (Zone 5) the so-called Marschalko type is a cell of moderate size and characterized by a relatively copious amount of cytoplasm deeply ultramarine blue in staining quality and coarsely granular and by a nucleus often eccentrically placed in which the densely aggregated chromatin masses tend to show a cart wheel formation There is as a rule just adjacent to the nucleus a narrow clear zone in sharp contrast to the opaquely blue cytoplasm The most immature form sometimes called lymphoblastic plasma cell (Schridde) or Turk's irritation form is here designated as plasmablast (Zone 3) which is provided with a typical cytoplasm but with an immature nucleus Again the cell showing a nuclear chromatin pattern of intermediate maturity the proplasmacyte (Zone 4) is often found in the tissues of such conditions as plasma cell leukemia (lymphadenosis leukemica plasmacellularis) or plasmacytoma (plasma cell myeloma) The plasmacytoid cell of Piney showing the presence of azurophilic granules in the cytoplasm is probably not a true plasma cell The cell sometimes referred to as virocyte (Liebowitz) appearing in the blood of patients suffering from viral infections is in all likelihood a true plasma cell

The plasma cells offer the greatest difficulty in establishing their respective positions in the developmental scale of hemocytes In the scheme here presented these cells are arranged in the order of their chromatin maturity thus not necessarily indicating their cytogenetic sequence Histologic evidences point to the lymphocytic origin of plasmacytes here indicated by the arrow signs across the sector line although it is probable that the plasma cell formation represents a type of cellular reaction involving the closely related cells of the blood as well as of the tissue including even the fibroblasts

Finally it must be stated that the foregoing discussion is intended only to be of some help in properly evaluating the blood pictures which the author has assembled in this Atlas and therefore is by no means to be considered an attempt to formulate any new theory of hemocytogenesis It merely represents an endeavor on the part of the author to redefine and reemphasize the blood cells that are of clinical importance and to rearrange them in proper genetic sequence according to a monophyletic conception

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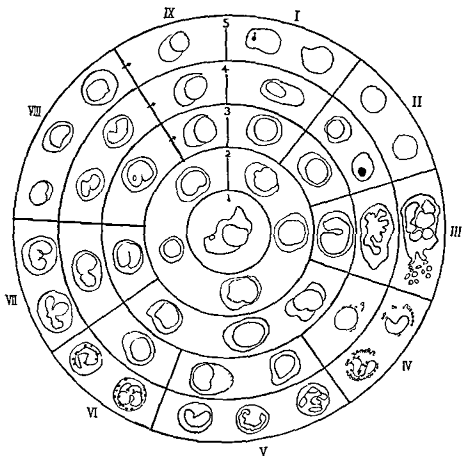
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PLATE 1

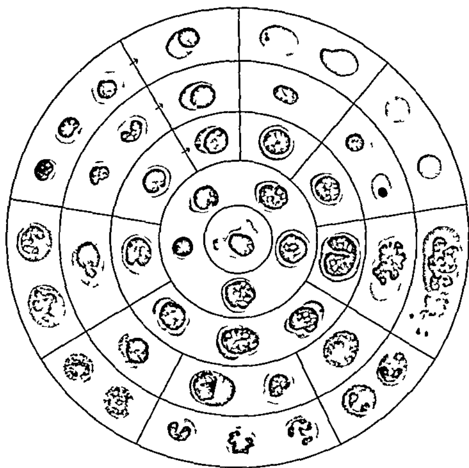
Monophyletic Theory of Hemocytogenesis



MONOPHYLETIC SCHEME OF HEMOCYTOGENESIS

This diagram (Plate 1) represents the author's monophyletic interpretation of the origin, differentiation and interrelationships of all blood cells, indicating the order of maturation in five well recognized stages (Zones 1-5 in concentric circles) of nine different cell groups (Sectors I-IX in clockwise order). The numerical references mentioned in Chapter 1 follow the order of cells as depicted in this plate.

Plate 1 Monophyletic Scheme of Hemocytogenesis



2 HEMATOPOIESIS IN THE EMBRYO AND FETUS

During the early stages of embryonic development the primitive connective tissue the mesenchyme functions as an omnipotential element constituting by far the greatest proportion of the embryonic body exhibiting an almost unlimited potentiality in differentiating into many varieties of specific tissue Like the quiescent type of the reticulo endothelial cell in the adult organism the primitive mesenchyme functions as the origin of all types of blood cells as well as of primitive endothelium In the numerous blood islands of the yolk sac the peripherally located cells form the walls of blood vessels while those centrally situated give rise to the first free cells of the blood here called hemocytoblasts

The earliest blood cells to develop from these stem cells are those of the primitive or fetal erythroid series the first trace of fetal hemoglobin (Hb F) becoming detectable in the late promegaloblast or early megaloblast The fetal red cells continue to multiply until the hepatic period of hematopoiesis is reached at approximately the third embryonic month which is followed by the myeloid period during the fourth or fifth month The definitive or adult type of red cells begin to be formed about this time gradually replacing the fetal cells although the primitive elements persist throughout the entire life of the fetus

In the early period (embryos up to 8 mm) the number of red cells has been estimated by Knoll to be 366 900 of which 92 per cent belong to the primitive series while at the end of the second month the figure decreases to 52 per cent the remainder belonging to the definitive type Since the primitive erythrocytes are large cells provided with a full quota of fetal hemoglobin the cell diameters vary from 8 5 to 10 5 microns with high concentrations of hemoglobin As the definitive erythrocytes replace the primitive forms both the cell volume and hemoglobin content are reduced correspondingly although the presence of nucleated erythrocytes often persists even until birth

The first leukocytes make their appearance relatively late in embryonic life In embryos of 12 to 18 mm in length (second month) Knoll found the white cell count to be about 1000 per cu mm of which 75 per cent belonged to the myeloid series The lymphocytes begin to appear in the peripheral blood during the fourth fetal month while the monocytes are not found until the fifth month

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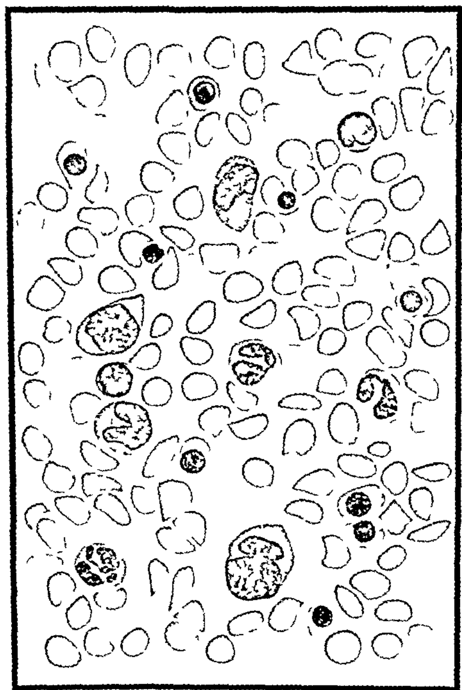
PLATE 2

Blood Picture of the Fetus

N	*Normocyte*
pN	Polychromatophilic normocyte
Ma	*Macrocyte*
Mi	Microcyte
oNb	*Orthochromatic* normoblast
pNb	*Polychromatophilic* normoblast
nPMy	Neutrophilic promyelocyte
nSg	Neutrophilic *segmentocyte*
M	Monocyte
mL	Mesolymphocyte

Plate 2 depicts the peripheral blood picture of a fetus at 5 months of gestation A large number of primitive erythrocytes and macrocytes well filled with fetal hemoglobin (Hb F) are found among smaller definitive normocytes The nucleated red cells appear to belong to the definitive series A tendency to monocytosis is also suggested

Plate 2 Blood Picture of the Fetus



3 THE BLOOD OF INFANTS AND CHILDREN

The blood p[illegible] following birth is characterized by macro cytosis and hyper[illegible] red cell the average diameters varying from 8 2u to 8 63 micr[illegible] hemoglobin content from 14 9 to 23 2 Gm per cent These values m[illegible] individual differences at first but the average adult levels are [illegible] within one month By using supravital staining technic the auth[illegible] the reticulocytes to be as high as 5 5 per cent in some cases soon after birth gradually falling to 1 0 per cent which is the normal adult average The peripheral blood of immature infants often contains nucleated red cells in [illegible] number and there seems to exist an inverse relationship between the numb[illegible] normoblasts in the blood and the degree of fetal maturity

The leuk[illegible] exhibit pictures that are more or less characteristic of different periods of growth In making total and differential counts in over 1000 infant and children the author found the total number to be markedly elevated (18 000–22 000 per cu mm) during the first 24 hours of life but dropped rather precipitously (9 000–10 000 per cu mm) on the third or fourth day After showing a light increase again at the end of the first week the count gradually fell to reach the adult level at 9–10 years of age

The striking leukocytosis seen in the neonatal period is due to the high proportion of granulocytes (65–70 per cent in the absence of any complications) The absolute number of lymphocytes at birth averages 4 000 per cu mm which after a temporary decrease on the fourth day may again rise to 6 000 during the succeeding four years gradually declining thereafter to the adult level of 3 000 per cu mm at puberty The most remarkable feature of the leukocytic picture in infancy is a great increase of monocytes (about 2 000 per cu mm) seen during the first four weeks of life which the author has called monocytosis neonatorum although its physiologic significance is entirely obscure The number of circulating thrombocytes during the early period of life has been estimated to vary from 150 000 to 250 000 per cu mm a range somewhat lower than that of older children and adults but the normal level is usually reached within 3–4 months

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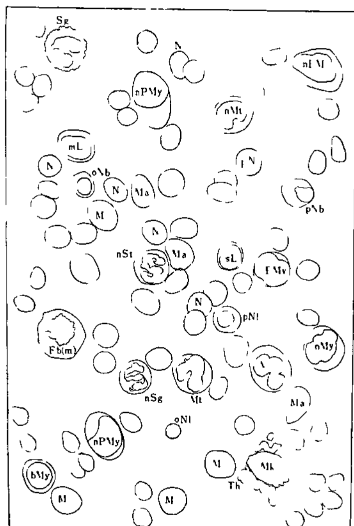
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PLATE 3

Blood Picture of the Newborn Infant

(1)



N	Normocyte
Ma	Macrocyte
nSt	Neutrophilic stab cell
nSg	Neutrophilic segmentocyte
eSg	Neutrophilic segmentocyte
M	Monocyte
sL	Small lymphocyte
Th	Thrombocyte

Plate 3 shows the peripheral blood cells of a newborn infant at 1.5 hours after birth. The majority of erythrocytes together with relatively numerous normoblasts are of the definitive series. A nuclear fragment of a megakaryocyte surrounded by a group of platelets is also noted. The presence of many immature leukocytes simulating a picture seen in myelogenous leukemia is not an infrequent finding.

Plate 3 Blood Picture of the Newborn Infant (1)

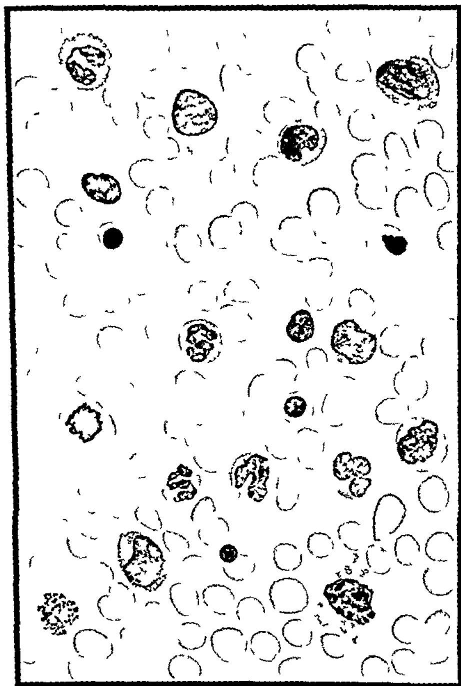
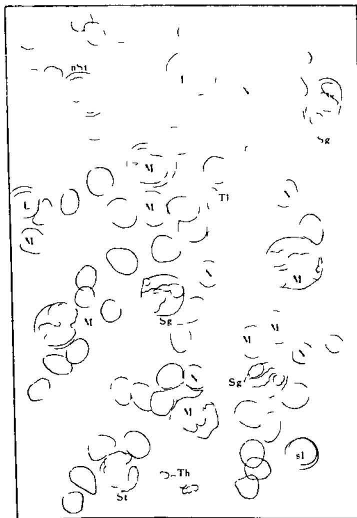


PLATE 4

Blood Picture of the Newborn Infant

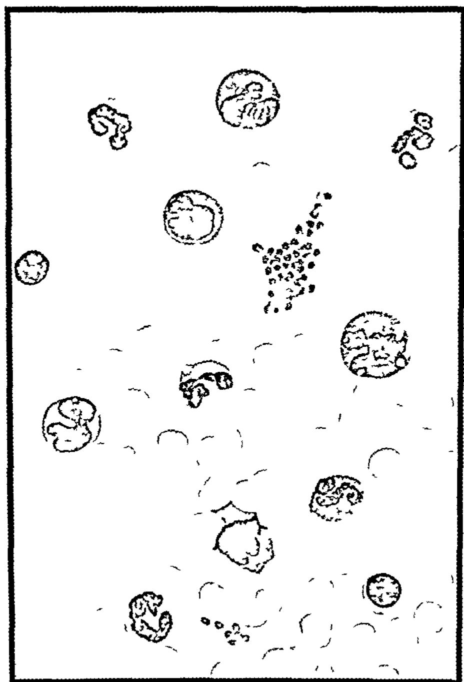
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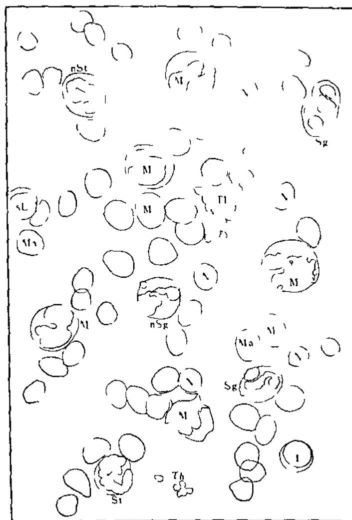


N	Normocyte
Ma	Macrocyte
nSt	Neutrophilic stab cell
nSg	Neutrophilic segmentocyte
eSg	Eosinophilic segmentocyte
M	Monocyte
sL	Small lymphocyte
Th	Thrombocyte

Plate 4 is the blood picture of a young infant on the third day of life The morphologic features of both red and white blood cells appear to be entirely normal signifying the complete maturity of the infant The monocytes in this blood were present to the extent of 24 per cent and this monocytosis neonatorum continued to exist for several weeks

Plate 4 Blood Picture of the Newborn Infant (2)

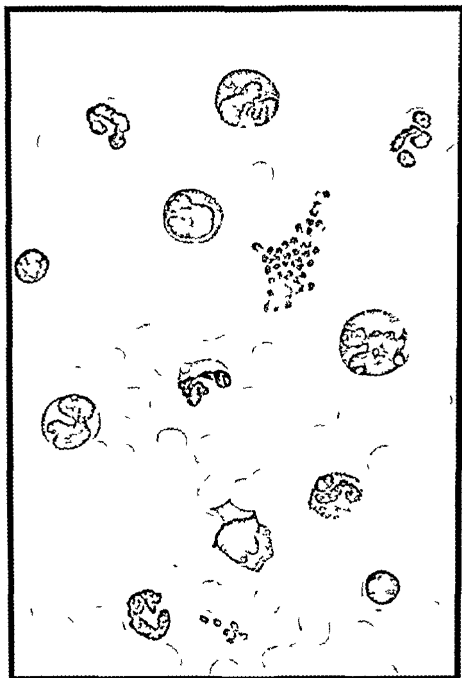




N	Normocyte
Ma	Macrocyte
nSt	Neutrophilic stab cell
nSg	Neutrophilic segmentocyte
eSg	Eo inophilic segmentocyte
M	Monocyte
sL	Small lymphocyte
Th	Thrombocyte

Plate 4 is the blood picture of a young infant on the third day of life The morphologic features of both red and white blood cells appear to be entirely normal signifying the complete maturity of the infant The monocytes in this blood were present to the extent of 24 per cent and this monocytosis neonatorum continued to exist for several weeks

Plate 4 Blood Picture of the Newborn Infant (2)



4 THE BONE MARROW IN CHILDHOOD

Marked variations are found in the bone marrow picture in childhood changing with the different periods of growth During the first few days of life Glasser Limarzi and Poncher noted a sharp decline in the percentage of erythroid cells attaining a stable level of about 23 per cent by the end of the first month The myeloid series on the other hand shows a tendency to increase slightly during the first two weeks gradually decreasing thereafter until a level of about 60 per cent is reached after one year The relation of the myeloid to the erythroid cells (M E ratio) is about 1 9 1 during the first two months after birth with the normal adult proportion of 3 6 1 not realized until puberty

Differential counts of the principal bone marrow cells made by the author on the smear preparations obtained from 51 normal infants and children ranging in age from 2 weeks to 15 years revealed the average values together with the limits of variations to be as listed below

Marrow cells	Range	Average
Myeloblasts	1 0— 3 0	2 0
Leukoblasts	2 0— 5 0	3 0
Neutrophils		
Promyelocytes	4 0—10 0	7 0
Myelocytes	8 0—12 0	10 0
Metamyelocytes	9 0—17 0	13 0
Staff cells	8 0—21 0	14 5
Segmentocytes	4 0— 7 0	5 5
Eosinophils		
Immature	2 0— 5 0	3 5
Mature	1 0— 3 0	2 0
Basophils		
All stages	0 0— 1 0	0 5
Monocytes	1 0— 3 0	2 0
Lymphocytes	14 0—24 0	19 0
Erythroblasts	1 0— 6 0	3 5
Normoblasts	15 0 —25 0	0 0

Myeloid Erythroid Ratio

1 2 Mo	3 12 Mo	1 2 Yr	3 4 Yr	5-6 Yr	7 10 Yr	11 15 Yr
1 9	2 1	2 3	2 4	3 7	3 4	3 6

The most striking feature of the bone marrow picture in childhood is the presence of heavily stained rounded nuclear masses in varying numbers closely resembling the small lymphocytes of the peripheral blood Most of these forms appear to be completely denuded only a few of them being provided with narrow rims of basophilic cytoplasm Their morphologic characteristics are suggestive of the condensed or pyknotic nuclei which were extruded from erythroid cells upon maturation It is conjectured that these elements may contain some essential materials such as nucleic acid derivatives vitally concerned in cell maturation and multiplication In other words these forms may be regarded as the pro-

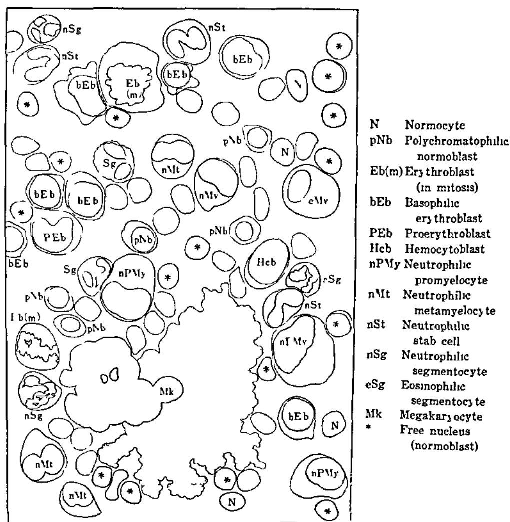


Plate 5 is the sternal marrow picture of a normal infant at 8 months of age Numerous dark staining and free lying spherical masses evidently the nuclei extruded from matured normoblasts are interpreted to constitute the hematogones capable of reproducing the normoblasts according to the homoplastic plan

Plate 5 Sternal Marrow Picture of the Infant (1)

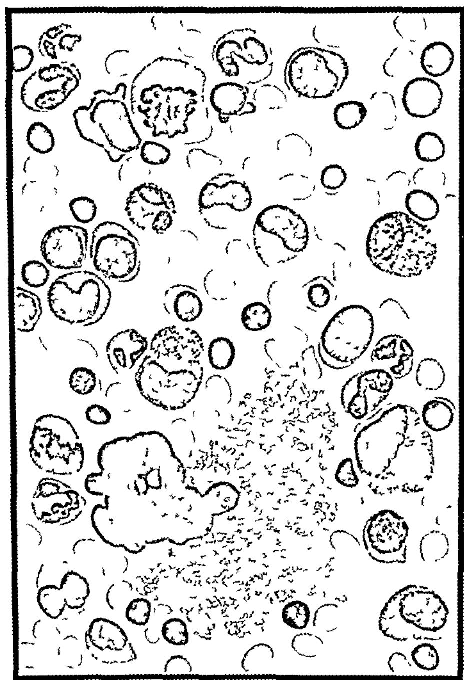
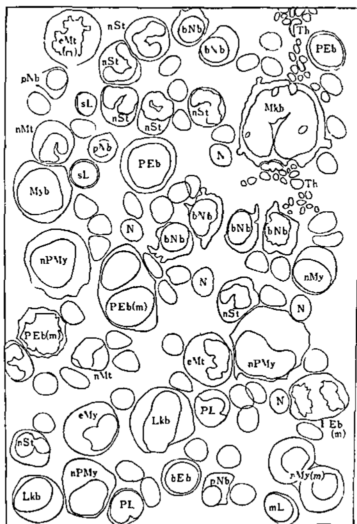


PLATE 6

Sternal Marrow Picture of the Infant

(2)



N	Normocyte
bNb	Basophilic *normoblast*
pNb	Polychromatophilic normoblast
PEb	Proerythroblast
PEb(m)	Proerythroblast (in mitosis)
Myb	Myeloblast
Lkb	Leukoblast
nPMy	Neutrophilic promyelocyte
nMy	Neutrophilic myelocyte (mitotic)
nMt	Neutrophilic metamyelocyte
nSt	Neutrophilic stab cell
eMy	Eosinophilic myelocyte
eMt	Eosinophilic metamyelocyte
eMt(m)	Eosinophilic metamyelocyte (mitotic)
Mkb	Megakaryoblast
sL	Small lymphocyte
mL	*Mesolymphocyte*
Th	Thrombocyte

Plate 6 represents the sternal marrow picture of a 14 month old infant illustrating an active hematopoiesis in both the erythrocytic and leukocytic series One megakaryoblast is seen which is already a huge cell showing an early tendency for nuclear segmentation even though the cytoplasm is yet completely basophilic and primitive

Plate 6 Sternal Marrow Picture of the Infant (2)



5 MEGALOBLASTIC ANEMIA OF INFANTS

Megaloblastic or macrocytic anemia of infants is a type of anemia resulting usually from defective nutrition more particularly from lack of vitamins and characterized by the presence of typical promegaloblasts and megaloblasts in the bone marrow frequently associated with thrombocytopenia and leukopenia However certain additional causative factors may be involved in producing this condition in infants such as congenital malformation of the gastrointestinal tract acute or chronic dyspepsia hepatitis sprue infection or hemolytic states Bilirubinemia and high plasma iron content found often in pernicious anemia of adults may also be demonstrated in this condition Hematologic findings as well as clinical signs indicate that the immature bone marrow of infants is inadequately prepared to meet the accelerated demand for blood occasioned by the rapidly growing body

This condition is seen most frequently in infants under 18 months of age with history of improper feeding as to nutritional and vitamin requirements The European literature contains reports of a similar type of anemia in infants on exclusive goat milk feeding The infant suffering from megaloblastic anemia presents the symptoms of malnutrition diarrhea and vomiting associated with slight enlargement of the liver and spleen Pallor or subicteric tinge of the skin lassitude irritability and intermittent fever often accompanied by respiratory or intestinal infection are commonly noted In severe cases hemorrhagic tendencies such as petechiae and frank bleeding may occur Cardiac enlargement with hemic murmurs may be demonstrated

Hematologically the findings are essentially identical to those of pernicious anemia but leukocytosis may be present if complicating infections intervene Macrocytosis is apparent on the smears of blood and bone marrow fluid but the red cells are characterized by marked anisocytosis and poikilocytosis The anemia may be moderate in degree although the color index may be relatively high despite the normal volume index Administration of vitamins particularly ascorbic acid folic acid and cyanocobalamine or liver extract is usually effective in producing a reticulocyte increase together with consequent improvement in the blood picture

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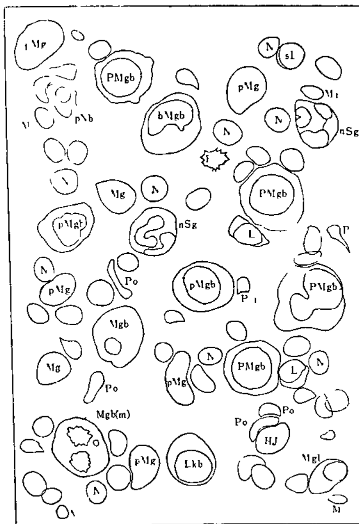
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PLATE 7

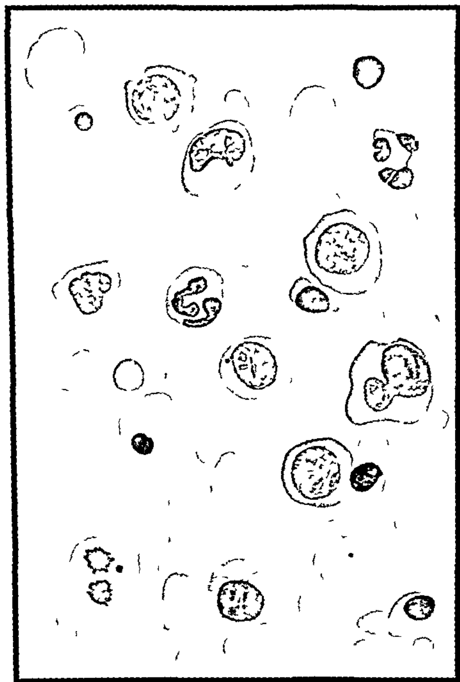
Megaloblastic Anemia of Infants



pNb	Polychromatophilic normoblast
Mg	Megalocyte
pMg	Polychromatophilic megalocyte
Mgb	Megaloblast
pMgb	Polychromatophilic megaloblast
PMgb	Promegaloblast
Mgb(m)	Megaloblast (in mitosis)
Mi	Microcyte
Poi	Poikilocyte
H J	Howell Jolly body
nSg	Neutrophilic segmentocyte
sL	Small lymphocyte

Plate 7 is the marrow picture of an infant 7 months in age which is characterized by the presence of many promegaloblasts and megaloblasts together with polychromatophilic macrocytes or megalocytes. The peripheral blood of this infant revealed a marked anemia with 2.18 million erythrocytes, 6.8 Gm. per cent hemoglobin and 21 per cent hematocrit value.

Plate 7 Megaloblastic Anemia of Infants



6 ERYTHROBLASTOSIS FETALIS

Erythroblastosis fetalis is a hemolytic disease of the newborn initiated during the last stage of intrauterine life and caused by excessive hemolysis due to the action of isohemolysin upon the fetal erythrocytes In accordance with the presenting symptoms the disorder may clinically be differentiated into hydrops fetalis with generalized edema icterus gravis neonatorum with profound jaundice or congenital anemia of the newborn with snow white pallor of the skin The etiologic mechanism of this disease was adequately explained in 1941 by Levine and his co workers who demonstrated the phenomenon of isoimmunization in the Rh negative pregnant mother by the Rh positive cells of the fetus This phenomenon may occur not only with the Rh blood factor but occasionally also with the group A or B factor in group O individuals It is furthermore clear that the erythroblastotic condition may arise from other factors capable of stimulating the formation of isoagglutinins such as injection of incompatible blood or even of bacterial toxoid in sensitive subjects

Although the three forms of this disease are distinguishable on the basis of their clinical manifestations all have these symptoms in common in varying degrees In hydrops fetalis the accumulation of fluid in tissues and body cavities leads to a monstrous appearance of the fetus and the child is often dead before birth or dies soon afterwards The infant with severe jaundice may survive if the symptoms are moderate but in the most severe cases hemorrhagic manifestations and cerebral signs may develop The mildest form of the disease is congenital anemia which usually responds well to adequate blood transfusions

Hematologically the presence of a large number of nucleated red cells in all stages of maturation can be demonstrated in the peripheral blood These cells are essentially normoblastic and rarely megaloblastic in morphologic character The red cell count may vary greatly from extreme oligocythemia to slight polycythemia with corresponding hemoglobin concentration The shape of the red cells deviates but little from normal but macrocytosis is apparent However the color index as well as the volume index tends to be greater than 1 0 while the saturation index is usually normal The high white cell count is compatible with the physiologic leukocytosis of the newborn period The icteric index may be remarkably high especially in the icterus gravis form (75–100 units) with increased serum bilirubin up to 30 mg per cent due to the elevation of the indirect fraction When Rh antibodies are involved the direct antiglobulin test of Coombs is strongly positive These findings may effectively be altered by means of exchange blood transfusion using Rh negative blood

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PLATE 8

Erythroblastosis Fetalis
(Icterus Gravis Neonatorum)

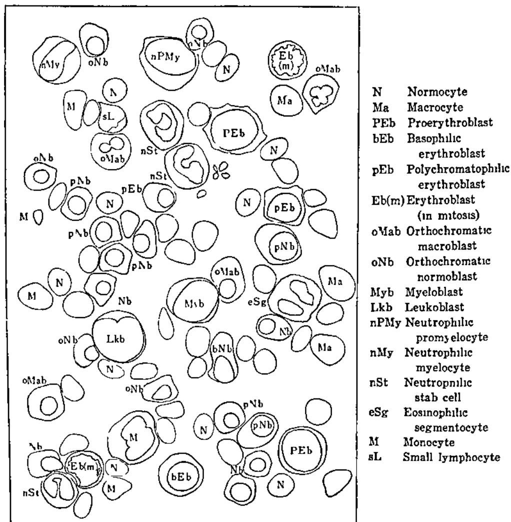


Plate 8 is the peripheral blood picture of icterus gravis neonatorum (erythroblastosis fetalis) in a newborn infant succumbing to the disease on the first day of life An accelerated erythropoiesis compensatory to increased hemolysis is apparent while the leukocytes exhibit a picture of leukemoid reaction

Plate 8 Erythroblastosis Fetalis (Icterus Gravis)

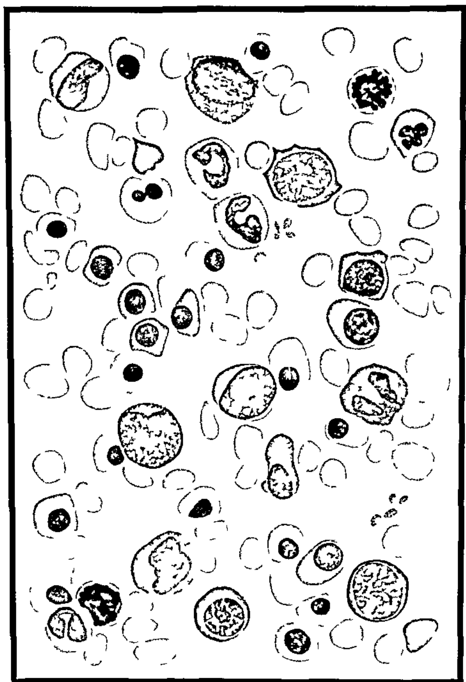
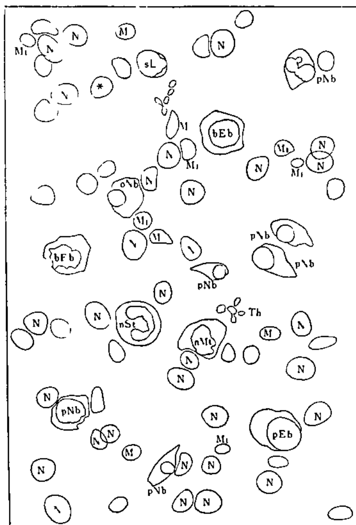


PLATE 9

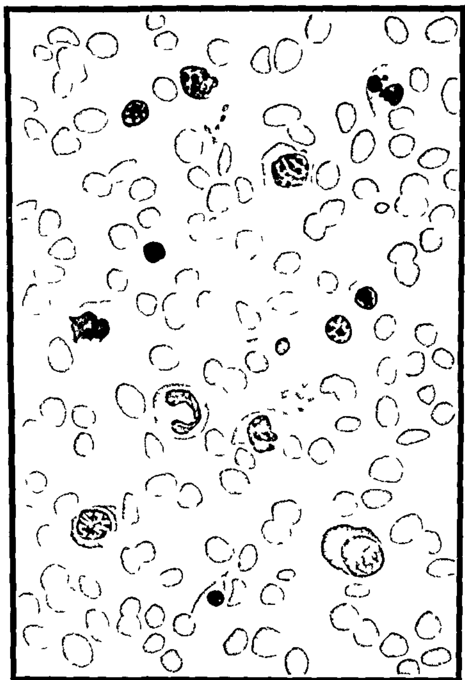
Erythroblastosis Fetalis
(Hydrops Fetalis)



N	Normocyte
Mi	Microcyte
bEb	Basophilic erythroblast
pEb	Polychromatophilic erythroblast
oNb	Orthochromatic normoblast
nMt	Neutrophilic metamyelocyte
nSt	Neutrophilic stab cell
sL	Small lymphocyte
Th	Thrombocyte
*	Extruded nucleus (normoblast)

Plat 9 illustrates the peripheral blood picture in hydrops fetalis or universal edema of the newborn (erythroblastosis fetalis) The presence of many normoblasts is characteristic as it is also in other forms of this disease

Plate 9 Erythroblastosis Fetalis (Hydrops Fetalis)



7 IRON DEFICIENCY ANEMIAS

As indicated by its designation iron deficiency anemia otherwise known as hypochromic microcytic anemia is a general name given to that group of anemic states arising basically from the disturbance of iron utilization for hemoglobin synthesis The condition is characterized primarily by the extreme reduction in the hemoglobin content of erythrocytes with some decrease in the cell volume although the number of cells is fairly normal The average diameter of red cells appears to be definitely decreased so that the individual cells are smaller because of the lesser amount of hemoglobin as compared with normal erythrocytes Such well known synonyms as nutritional hypochromic anemia chloranemia chlorosis asiderotic anemia and primary or chronic hypochromic anemia have been applied to this type of anemia

Erythropoiesis under physiologic conditions represents a complex mechanism requiring a variety of building materials of which iron is of major importance Iron balance in the body is maintained only when the source medium and chemical reactivity of ingested iron are in their optimal relationship with reference to the excretory function Iron transport takes place in the plasma by combining with a carrier protein β globulin and the combined form is usually called transferrin or siderophilin The normal values of plasma iron have been found to vary *from 50 to 180 micrograms per cent a range of 80–120 being most common* and this level is definitely lowered in iron deficiency anemia It is also important to remember that iron once absorbed is excreted with difficulty only approximately 27 mg being normally absorbed and excreted in 24 hours

Iron utilization after the metal is ingested depends on the ease with which it can be mobilized from the storage depot or labile iron pool Iron is stored in this depot in the form of ferritin a combined product of ferric hydroxide with a protein apoferritin There is in addition another form of iron storing compound hemosiderin which can be demonstrated as visible particles in aspirated marrow materials Likewise the amount of siderotic granules present in the sideroblasts may also furnish further information regarding the availability of iron in the bone marrow

(1) **Chlorosis** is a form of iron deficiency anemia seen mostly in young girls at puberty and adolescence and its synonym green sickness originated from the greenish yellow tinge of the skin commonly observed in affected individuals The condition was first described as a clinical entity (De morbo virgineo) by Lange in 1520 and classified as a disease of the blood for centuries until Fowler in 1936 wrote an obituary of this disease While numerous factors have been mentioned in the etiology of this disorder it is sufficient to consider the defect in iron balance brought about chiefly by maladjusted blood loss due to menstruation Dietary idiosyncrasies and emotional disturbances often associated with the menarche may constitute the contributory factors The fact that the incidence of the disease has shown a remarkable decline with the improvement in living condition is etiologically significant

(2) **Chronic hypochromic anemia** refers to a type of iron deficiency anemia developing as a result of prolonged negative iron balance occurring more commonly in women than in men in the third to fifth decades of life and characterized by achlorhydria mild glossitis koilonychia sideropenic dysphagia and acroparesthesia Numerous synonyms for this disease are found in the literature

including simple achlorhydric anemia achylic chloroanemia late chlorosis and essential primary or idiopathic hypochromic anemia It was the association of simple anemia with chronic achylia gastrica which led Faber in 1913 to regard this disease as a nosologic entity

Hematologically extreme hypochromia of the red cells is so generalized that practically all cells show central pallor and the hemoglobin is deposited only as a thin ring around the periphery The mean corpuscular hemoglobin concentration is far below normal accompanied by some reduction in the packed cell volume although the cell count is little affected The average erythrocyte diameter varies from 6 to 6 5 microns Plasma iron is naturally decreased but plasma copper is usually high Neither leukocytes nor thrombocytes show significant changes The bone marrow is characterized by a normoblastic hyperplasia due to an increase in the percentage of small polychromatophilic normoblasts and the rate of proliferation roughly parallels the degree of anemia

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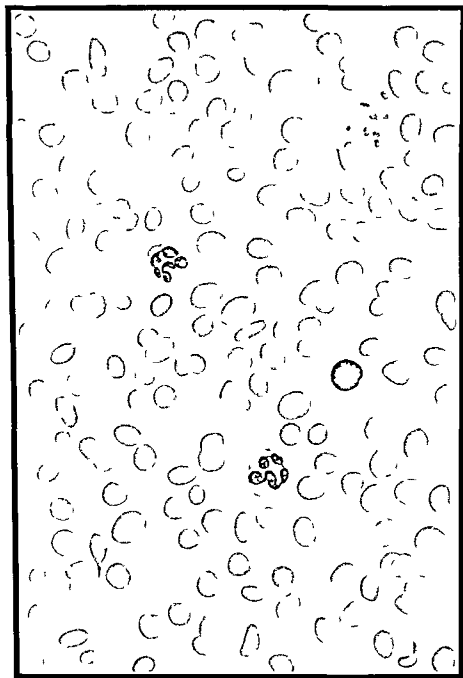
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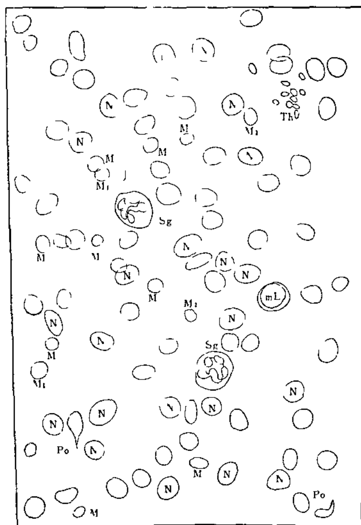
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PLATE 10

Chlorosis

Plate 10 Chlorosis





N	Normocyte
Mi	Microcyte
nSg	Neutrophilic segmentocyte
mL	Mesolymphocyte
Th	Thrombocyte

Plate 10 delineates the typical blood picture in chlorosis a term which is little used at present The condition is essentially a form of iron deficiency anemia most frequently seen in young patients the red cells being characterized by anisocytosis microcytosis and hypochromia while the white cells show practically no change

Plate 10 Chlorosis

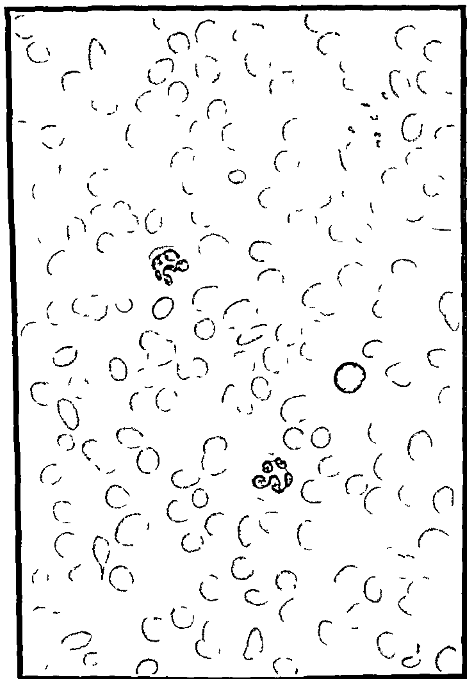


PLATE 11

Primary Hypochromic Anemia of Women

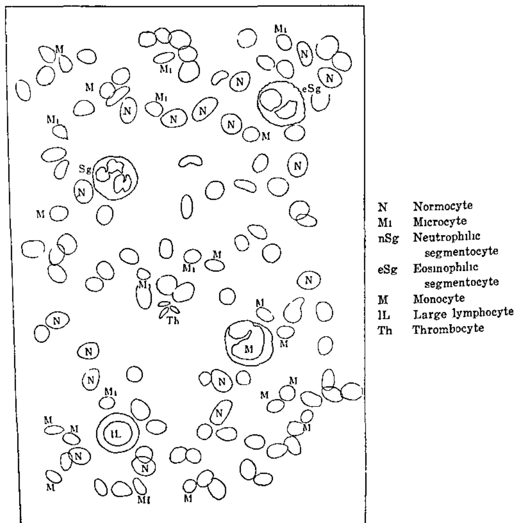
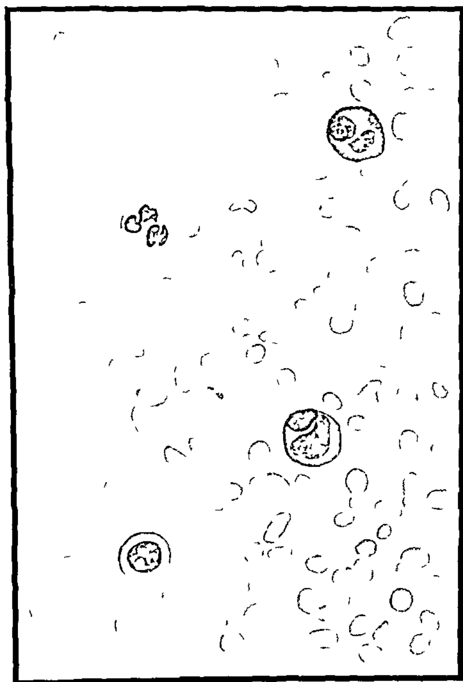


Plate 11 represents the peripheral blood picture in a typical case of primary hypochromic anemia of women characterized by extreme microcytosis aniso cytosis and hypochromia of the red cells The color and volume index values are usually very low both being reduced to approximately 0 5

Plate 11 Primary Hypochromic Anemia



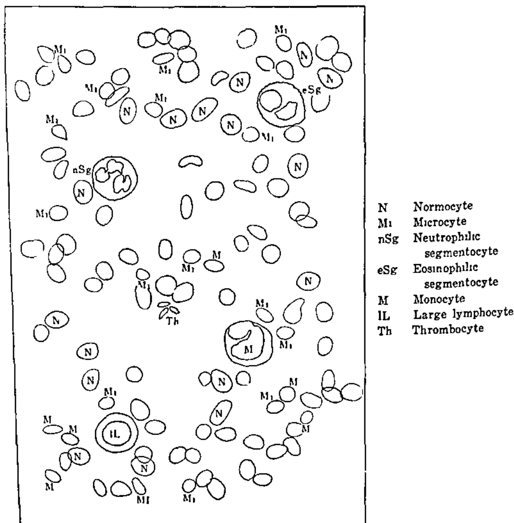


Plate 11 represents the peripheral blood picture in a typical case of primary hypochromic anemia of women characterized by extreme microcytosis anisocytosis and hypochromia of the red cells The color and volume index values are usually very low both being reduced to approximately 0 5

8 REFRACTORY ANEMIAS

Refractory anemias comprise a group of severe anemias usually associated with extreme leukopenia particularly granulocytopenia and distinct thrombocytopenia These conditions are so named because of their unknown etiology and the known methods of treatment are either completely or only temporarily effective in producing clinical as well as hematologic improvement The two most important varieties of this group are aplastic or primary refractory anemia and congenital hypoplastic anemia In all likelihood such terms as progressive hypocythemia aregenerative anemia aleukia hemorrhagica panmyelophthisis idiopathic aplastic anemia and similar designations found in the literature are often used synonymously for the conditions here referred to

(1) **Aplastic anemia** was first described in 1888 by Ehrlich who noted not only the severe anemia but also profound changes in the bone marrow While anemia is the most outstanding feature of this disease all other formed elements of the blood are greatly depressed in number so that the condition is characterized by a veritable pancytopenia based on the extreme degree of panmyelophthisis The bone marrow is found to be almost completely acellular associated with fatty or gelatinous degeneration In addition to the primary type with unknown etiology there are cases of secondary aplasia developing as a result of overdosage of radiation or of contact with hemotoxic chemicals

The disease occurs frequently in young adults characterized by indefinite symptoms in the early stage but later by the progressive manifestation of palpitation dyspnea hemic murmurs and finally a hemorrhagic tendency Extreme granulocytopenia is conducive to infections particularly of the oral mucosa Cardiac hypertrophy may be noted but lymphadenopathy or splenohepatomegaly is rare While the treatment is purely symptomatic and protective some improvement may be expected from splenectomy under certain circumstances

(2) **Congenital hypoplastic anemia** is most frequently seen in children and the early symptoms may appear during the first three months of life This suggests a possible hereditary cause although no evidence of the disease has yet been discovered in the family history Diamond and Blackfan after making an extensive study of this disease inferred that the mechanism of its production may involve a congenitally abnormal metabolism of certain substances vitally concerned in hematopoiesis possibly blood pigments and amino acids Other synonyms used in the literature include chronic congenital aregenerative anemia erythrogenesis imperfecta and true red cell aplastic anemia

Like primary refractory anemia the onset of this disorder is insidious such vague complaints as facial pallor anorexia lassitude and sleeplessness being most common As the disease progresses dyspnea palpitation and cardiac enlargement with hemic murmurs can usually be demonstrated but hemorrhagic manifestations are never encountered The condition is characterized by its chronic course with little change in clinical symptoms and the ultimate prognosis is uncertain Blood transfusions are effective in bringing about clinical as well as hematologic improvement and under proper management the patient is able to carry on an entirely normal life

The blood picture is that of almost pure red cell aplasia but the anemia is normocytic and normochromic in type because of the corresponding decrease in hemoglobin content of the blood The bone marrow is deficient in normoblasts

PLATE 12

Aplastic Anemia

despite its apparent cellularity Leukopenia when present is only moderate the granulocytes being the type most frequently involved The thrombocytes may also be decreased in some cases

In repeating blood transfusions in these patients the donor blood should be carefully examined not only as to ABO compatibility but also in regard to MN and Rh Hr types in order to minimize the possibility of antibody formation in the recipient The use of pertinent vitamins and hematinics is always indicated whenever the patient s symptoms demand

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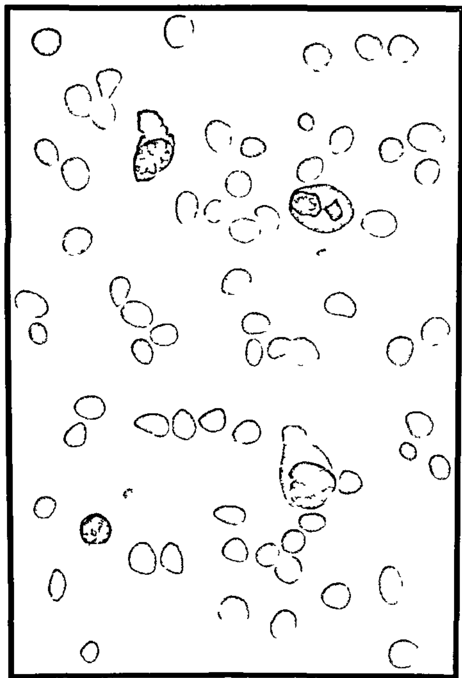
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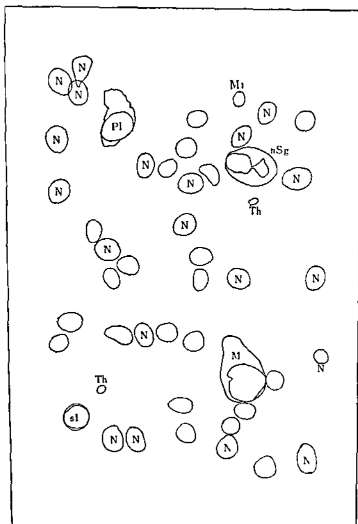
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Plate 12 Aplastic Anemia





N	Normocyte
Mi	Microcyte
nSg	Neutrophilic segmentocyte
M	Monocyte
sL	Small lymphocyte
Pl	Plasmacyte
Th	Thrombocyte

Plate 12 delineates a typical picture of the peripheral blood in aplastic (are generative) anemia occurring in a 5 year old female child Aplasia involves all formed elements of the blood and the diagnosis was confirmed at autopsy by finding a gelatinous transformation of the bone marrow

9 HEMOTOXIC AND MYELOTOXIC ANEMIAS

Hemotoxic and myelotoxic anemias mostly hemolytic in nature develop in individuals who are abnormally hypersensitive to chemical physical or biologic agents especially when the doses administered are excessive A great variety of medicinal preparations may also produce hemolytic anemia because of their injurious effects on the circulating erythrocytes as well as on the hemopoietic organs It has often been stated that the drugs containing benzene rings in their chemical structures are most likely to act as blood poisons Of the physical agents thermal burns of severe degree involving a wide area of the body may produce accelerated hemolysis associated with dyshemopoiesis Ionizing radiation may induce hemolytic anemia although its primary effect appears to be that of bone marrow aplasia Bacterial and viral infections as well as certain vegetable and animal poisons are also important and potent factors in the etiology of hemotoxic anemias

The exact mechanisms operative in producing hemolytic anemia under various conditions of intoxication are not fully understood but it is presumable that the factors involved must be multiple and quite complex in nature Although the noxious agents may possibly exert a direct action upon the erythrocytes in the circulating blood it is more likely that the effect is rather indirect by way of autoimmunization with the patient s own erythrocytes serving as an antigen after being subjected to the influence of the toxic material The literature has been reviewed by Wintrobe who lists the following chemicals as most frequently concerned phenylhydrazine naphthalene trinitrotoluene benzene nitrobenzene acetanilid phenacetin saponin lecithin promin methyl chloride allyl propyl disulfide (oil of onion) arsine lead and colloidal silver Recent tendencies in the intensified use of new compounds including carcinogenic and anticarcinogenic substances are significant in this respect The radioactive contamination of food water and air now being demonstrated to be increasing in degree and extent constitutes in all likelihood the greatest hazard in the causation of anemia and marrow aplasia

Lead poisoning refers to a state of intoxication produced by the toxic action of lead inducing a type of hemolytic anemia accompanied by profound disturbance in the mechanism of erythropoiesis particularly of hemoglobin synthesis The acute form of poisoning has been observed in cancer patients receiving lead therapy resulting in progressive anemia with reticulocytosis together with appearance of many red blood cells showing basophilic stippling In chronic lead poisoning such as the type formerly observed in Japanese nurslings on maternal milk feeding the affected infants either ingested the metal in toxic amounts through the milk or came in direct contact with the lead containing cosmetics used by the mother In severe cases some of these infants developed symptoms of lead encephalopathy and the condition was once thought to be even a benign form of meningitis (Kato 1932)

Acute plumbism is rare but the chronic type is frequently encountered among individuals who are more or less constantly exposed to lead in their occupation The metal after entering the body is deposited as a rule at the ends of long bones so that the shadows of the epiphyseal lead lines can be readily identified on the roentgeogram The gingival lead lines are seen at the edge of the gums immediately opposite the teeth appearing as a row of dots or vertical streaks

PLATE 13

Anemia due to Infection

made up of bluish black lead sulfide The skin often presents a yellowish tinge due to the presence of bilirubinemia and coproporphyrin III is excreted in the urine in abnormally large amounts

In mild cases the only sign of poisoning may be the presence of red blood cells with basophilic stippling as pointed out by Takasu in 1906 The mechanism operative in the formation of these stippled cells has not been fully elucidated but it is probable that the granules represent free ionized iron and hence the stippled cells may be considered to be the siderocytes or sideroblasts It has furthermore been inferred that the toxic effect of lead manifests itself upon the mechanism of heme synthesis and upon the function of the porphyrin forming tissues

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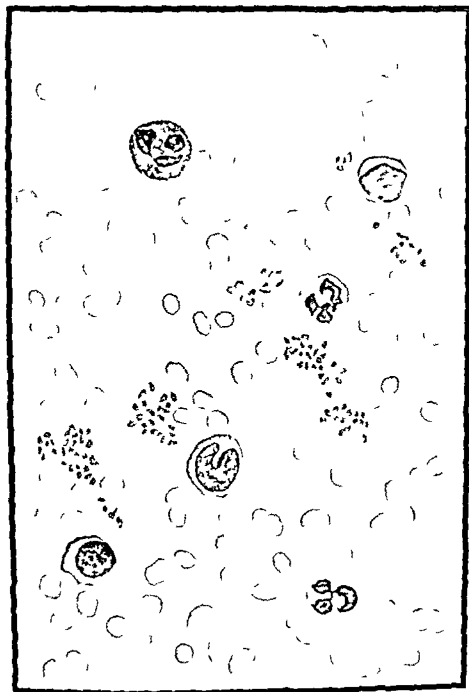
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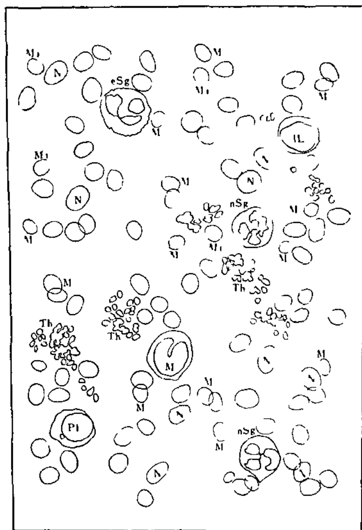
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Plate 13 Anemia due to Infection





N	Normocyte
Mi	Microcyte
nSg	Neutrophilic *segmentocyte*
eSg	Eosinophilic segmentocyte
M	Monocyte
lL	Large lymphocyte
Pl	Plasmacyte
Th	*Thrombocyte*

Plate 13 depicts the blood picture microcytic in type of an infant 11 months old with a marked cervical adenopathy Blood examination revealed the red cell count to be 4 600 000 but the hemoglobin content was only 8 9 Gm per cent with the packed cell volume 33 per cent A slight leukocytosis of 13 000 was present

Plate 13 Anemia due to Infection

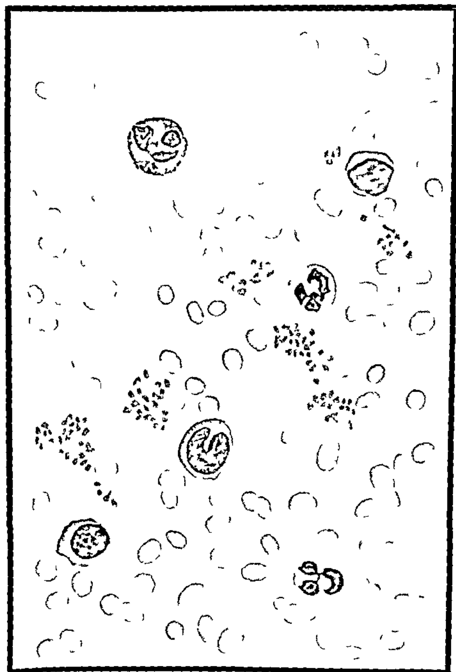


PLATE 14

Lead Poisoning

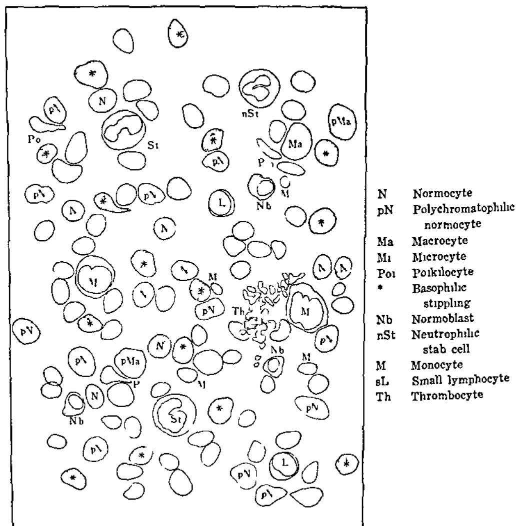


Plate 14 illustrates a case of lead poisoning in a painter's son who was fond of licking lead containing white paint This picture was obtained on admission to the Bobs Roberts Hospital (University of Chicago) under the diagnosis of lead encephalopathy The presence of a large number of erythrocytes with basophilic stippling is pathognomonic

Plate 14 Lead Poisoning

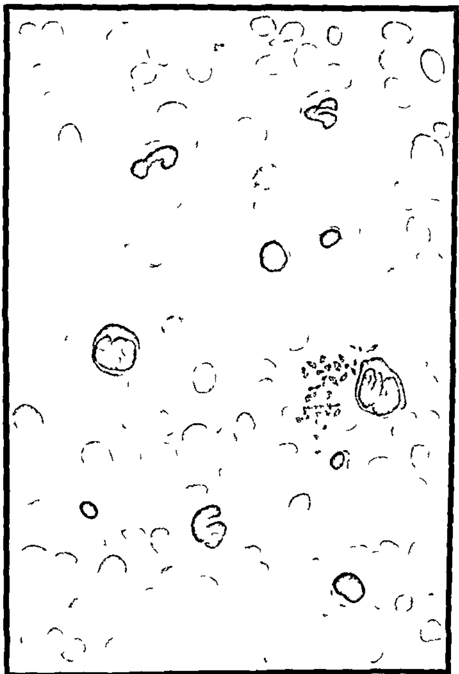
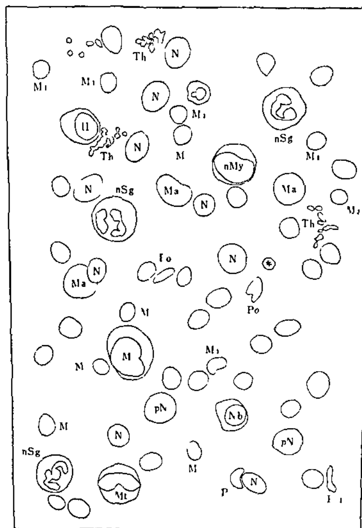


PLATE 15

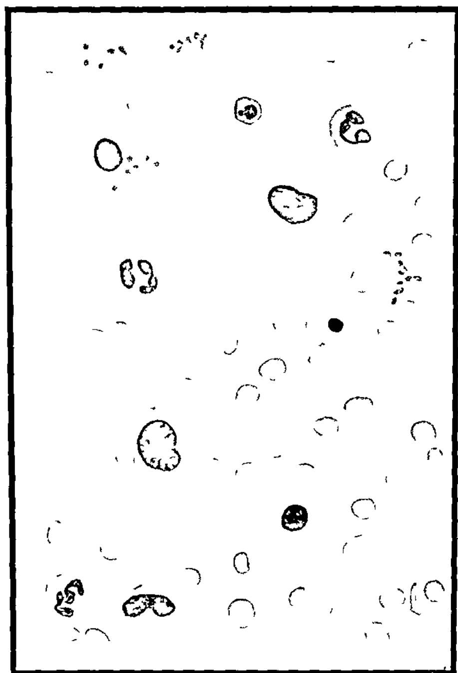
Sulfanilamide Intoxication



N	Normocyte
Ma	Macrocyte
Mi	Microcyte
pN	Polychromatophilic normocyte
Poi	Poikilocyte
*	Free nucleus of normoblast
Nb	Normoblast
nMy	Neutrophilic myelocyte
nMt	Neutrophilic metamyelocyte
nSg	Neutrophilic segmentocyte

Plate 15 is the blood picture of *severe anemia in prontolyn intoxication* characterized by a marked anisocytosis with microcytosis as a prominent feature. The presence of a few normoblasts and polychromatophilic normocytes indicates a moderate acceleration of erythropoiesis. A tendency for granulocytic immaturity is also noteworthy.

Plate 15 Sulfanilamide Intoxication



10 POIKILOCYTOSIS AND POIKILOCYTIC ANEMIA

Poikilocytosis refers to an alteration in the shape and configuration of red blood cells so that instead of being round or slightly oval they assume a variety of irregular and bizarre forms This phenomenon differs from crenation or thorn apple appearance of the cells which is usually produced artificially by physical or chemical means In certain cases of chronic infection and hemolytic anemia poikilocytosis may be an outstanding hematologic finding Since poikilocytes are frequently encountered and abundantly present in association with anemic states of undetermined etiology the author considers the designation of poikilocytic anemia [illegible] not entirely inappropriate Rous and Robertson (1917) pointed out th[illegible]tosis is one of the morphologic evidences of accelerated red cel[illegible] the fragmentation of these cells is assumed to be the ch[illegible] mechanism involved in the process of hemolysis However it is often difficult to understand why so many erythrocytes of this type are present in the blood when there is little evidence of increased hemolysis in poikilocytic anemia

In regard to the mechanism operative in the production of poikilocytes only a few scattered accounts of experimental observations are available in the literature Some of the older investigators (Neumann 1865 Pollett 1870) endeavored to test the effect of electric current on the shape of the red cells while others (Kanellis 1927 Nicolaeff 1930) explored the influence of certain chemical substances particularly lecithin cholesterol and alanin It is quite conceivable that the suspension medium plays an important part in regulating the shape of the red corpuscles as do also certain phy ical factors and different stresses However since the poikilocytes irregular and bizarre shapes apparently develop while they are still in the bone marrow there is a possibility that certain conditions inherent in the red cells themselves are responsible in producing the phenomenon

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PLATE 16

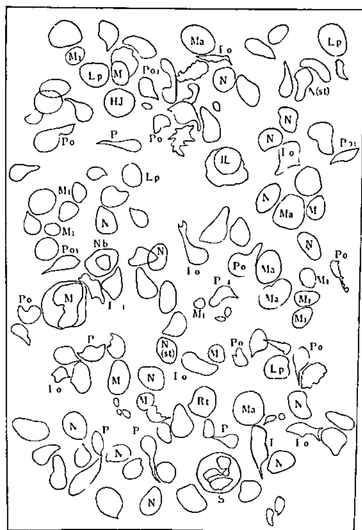
Poikilocytic Anemia

(1)

den rothen Blutkorperchen hervorbringen Sitsungsber Wien Akad Math Naturwis Kl 50 Abt 2 1865
Rous P and Robertson O H The normal fate of erythrocytes I The findings in healthy animals J Exper Med 25 651 1917

Plate 16 Poikilocytic Anemia (1)





N	Normocyte
Ma	Macrocyte
Mi	Microcyte
Poi	Poikilocyte
Rt	Reticulocyte
Lp	Leptocyte
N(st)	Stippled normocyte
Nb	Normoblast
H J	Howell Jolly body
nSg	Neutrophilic segmentocyte
M	Monocyte
IL	Large lymphocyte

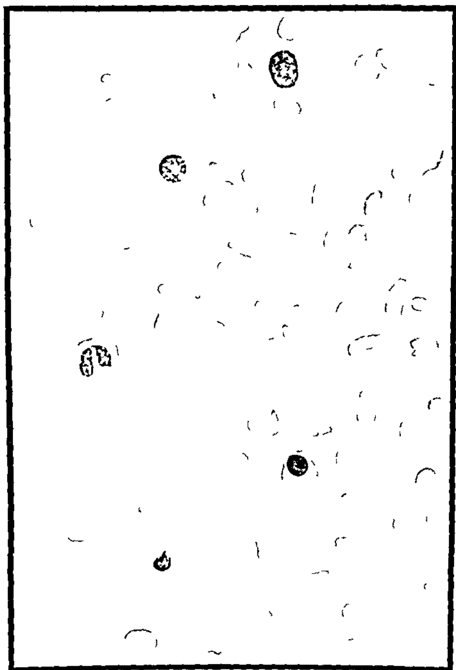
Plate 16 illustrates a blood picture which is tentatively designated as poikilocytic anemia seen in a 23 year old male patient The predominance of poikilocytes associated with marked anisocytosis and together with the occurrence of a few normoblasts and stippled red cells constitute the unusual features of this blood

PLATE 17

Poikilocytic Anemia

(2)

Plate 17 Poikilocytic Anemia (2)



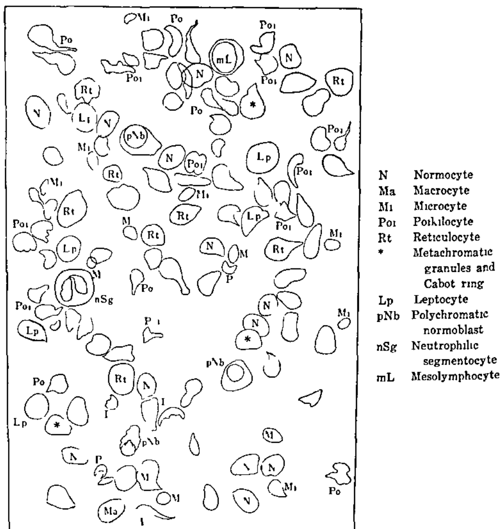


Plate 17 is the peripheral blood picture in poikilocytic anemia of five years duration in a 13 year old female child The striking features of the blood are the presence of numerous bizarre poikilocytes a few red cells containing Cabot ring bodies and a fair number of reticulocytes (Courtesy of Dr H Bakwin)

11 ELLIPTOCYTOSIS (OVALOCYTOSIS)

Elliptocytosis or ovalocytosis refers to a condition of the blood characterized by the excessive presence of elongated erythrocytes with rounded ends but producing no particular ill effect to the individuals affected In freshly prepared suspension 60 to 90 per cent or more of the red cells may show this peculiar shape although the degree of ovalocytosis appears to increase on standing in vitro Morphologically these abnormal cells may vary from the long narrow and rod shaped type (12×3 microns) to the oval type (11 5×6 0 microns) or almost round (8 25×6 microns) Isaacs (1938) stated that the form of the cell seems to be bound up with the stroma so that the shape remains unchanged in hypertonic isotonic or hypotonic solution or in normal serum Despite these findings however the condition has been found to be associated with signs of accelerated hemolysis in about 12 per cent of cases with ovalocytosis Unless increased blood destruction is adequately compensated by increased blood production hemolytic disease with anemia may be the result

The condition is said to be an essentially hereditary anomaly—first described by Dresbach (1904) and later observed by many others—the trait being transmitted as a simple mendelian dominant affecting both sexes and many races The phenomenon may appear in successive generations in a family although some offspring may have entirely normal red corpuscles (Grzegorzewski 1933) In affected individuals the abnormal cells are found in the bone marrow the first suggestion of the trait being observed in the reticulocytes but not in the nucleated forms The degree of ellipticity appears to increase with the growth of the child after birth up to about four months when the number of fully established elliptocytes seems to become stabilized Elliptocytosis must be differentiated from sicklemia on morphologic grounds although these two conditions have been considered to represent gradations of the same phenomenon (Pollock and Dameshek 1934) Hereditary elliptocytosis is to be distinguished from symptomatic ovalocytosis the former being characterized by the abnormally increased number of truly elliptical red cells the latter by the presence of mostly oval type

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PLATE 18

Elliptocytosis

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Plate 18 Elliptocytosis



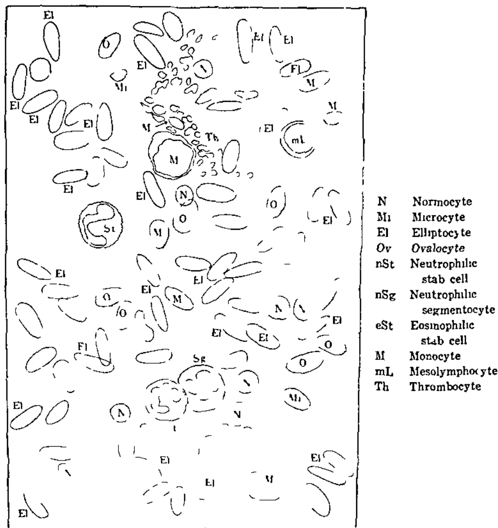


Plate 18 represents the blood picture in a case of ovalocytosis (elliptocytosis) which is usually considered to be a familial and hereditary condition The eccentricity of an elliptocyte may be calculated from the longest and the shortest diameters of the cell

Plate 18 Elliptocytosis



12 THALASSEMIA

Cooley's Anemia

Thalassemia is a hereditary and familial disorder of the blood characterized by progressive anemia beginning early in life associated with pronounced erythroblastemia and hepatosplenohepatomegaly and striking changes of bones. The condition was first clearly delineated by Cooley and Lee in 1925 from a somewhat ill defined group of severe and usually fatal anemias occurring in infancy and childhood known as anemia infantum pseudoleukemica (von Jaksch-Hayem-Luzet) in the older literature. Other synonyms commonly employed are Cooley's erythroblastic anemia, Mediterranean anemia and hereditary leptocytosis. The anerythroblastic type seen in adolescents and adults has been described by Dameshek under the name of target-cell anemia. What Strauss and his co-workers call familial microcytic anemia may represent a mild form of thalassemia. It is customary to recognize two forms of this disease thalassemia major and thalassemia minor the former corresponding to the homozygous and the latter to the heterozygous state while the completely benign form is referred to as thalassemia minima or microcythemia.

The hereditary nature of the disorder has gradually been unfolded and the mode of inheritance now appears to be a type of autosomal recessive or due to the simultaneous appearance of two allelomorphic genes. The clinical manifestations therefore depend on the genetically determined defect in erythropoiesis so that the red cells are provided with an excessive membrane but contain very little hemoglobin. The cells are extremely thin (leptocytes) while their osmotic resistance is increased. The presence of a relatively large amount of fetal hemoglobin (Hb F) may represent a primary effect of the thalassemia gene preventing the formation of adult hemoglobin (Hb A). The thalassemia gene may combine with other traits by simultaneous heterozygosity to produce sickle cell thalassemia or microdrepanocytic disease, hemoglobin C thalassemia and hemoglobin E thalassemia.

The earliest signs of thalassemia consist of pallor and gradually increasing circumference of the abdomen due to splenomegaly which eventually may attain an enormous dimension. The retardation of physical and mental development mongoloid facies with subicteric tinge of the skin are characteristic. The heart is enlarged and hemic murmurs may be heard. Effusions into the body cavities and ecchymoses as well as free bleeding may occur. The most unique changes develop in the cranial bones, consisting of a remarkable thickening of the diploe of the skull with numerous perpendicular striations between the outer and inner tables which give a roentgenologic hair on end appearance. In the long bones the medullary space is widened and presents a mosaic pattern of increased trabeculations. The disease progresses uninterruptedly and death comes usually as a result of intercurrent infection.

Hematologically the peripheral blood is characterized by severe anemia, with variable red cell counts and a marked reduction in cell volume and hemoglobin content. This anemia is essentially hypochromic and microcytic with a decided tendency to leptocytosis and poikilocytosis. The irregular distribution of hemoglobin in the target cell is marked by the formation of a circular island of the pigment usually situated at the center of the cell which may or may not show a connecting bridge stretching to the thin layer of the periphery. Again there may be other leptocytes presenting an appearance of wavy furrowed or ridged

distribution of the pigment so as to form a complex network within the cells Polychromatophilia and reticulocytosis are also prominent The presence of immature cells of the erythroid series representing all stages of maturation in the circulating blood is another peculiarity and the morphologic study of these forms was made by Kato and Downey in 1933

Evidences of well marked myeloid stimulation are demonstrated by the occurrence of distinct leukocytosis accompanied by a fair number of myelocytes metamyelocytes and even a few myeloblasts Such a picture has led some observers to call it pseudoleukemic but it is more appropriate to regard it as a form of leukemoid reaction The bone marrow cytology fully substantiates all of the hematologic characteristics of this disease

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PLATE 19

Anemia Infantum Pseudoleukemica
(von Jaksch Hayem)

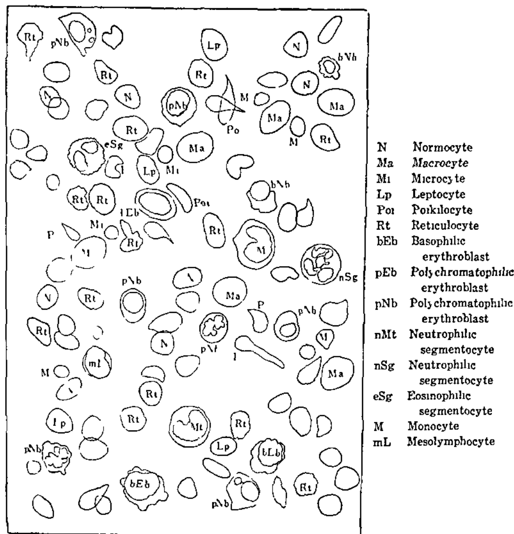


Plate 19 is the blood picture seen in anemia infantum pseudoleukemica (von Jaksch Hayem) Numerous normoblasts with pyknotic nuclei some being stippled while others contain Howell Jolly bodies clearly speak for accelerated erythro poiesis Marked anisocytosis moderate poikilocytosis and polychromatophilia characterize the red cells

Plate 19 Anemia Infantum Pseudoleukemica

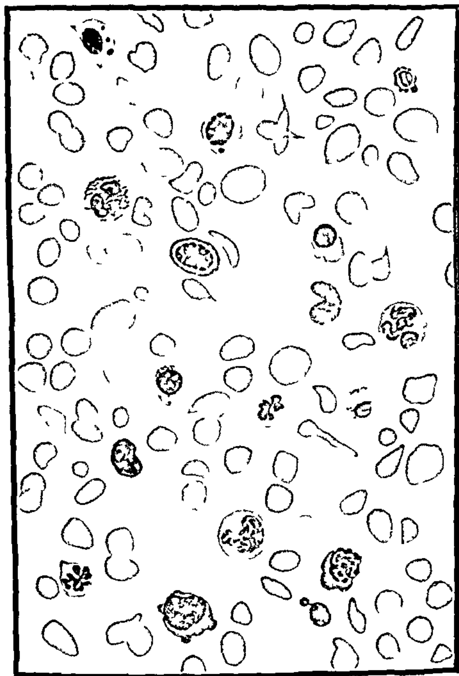
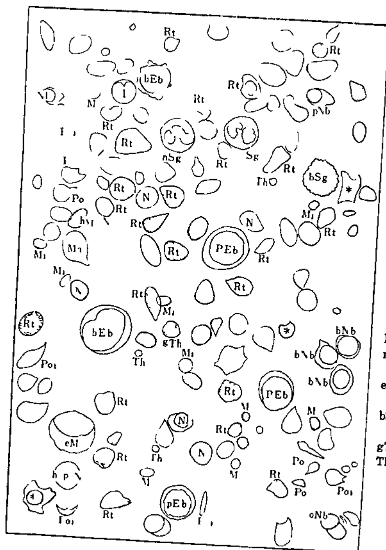


PLATE 20

Erythroblastic Anemia

(1)



N	Normocyte
hypoN	Hypochromic normocyte
Ma	Macrocyte
Mi	Microcyte
Poi	Poikilocyte
*	Unusual poikilocyte
Rt	Reticulocyte (anisocytosis)
Nb	Normoblast
bEb	Basophilic erythroblast
PEb	Proerythroblast
nSg	Neutrophilic segmentocyte
eMy	Eosinophilic myelocyte
bSg	Basophilic segmentocyte
gTh	Giant thrombocyte
Th	Thrombocyte

Plate 20 is the peripheral blood picture seen in a 6 month old infant with erythroblastic anemia (Cooley). The blood was first treated with brilliant cresyl blue in normal saline with the smear stained by the May Grunwald technic The changes characteristic of this disease are seen in the red as well as the white cells The reticulocytes are particularly well brought out by the supravital pretreatment

Plate 20 Erythroblastic Anemia (1)

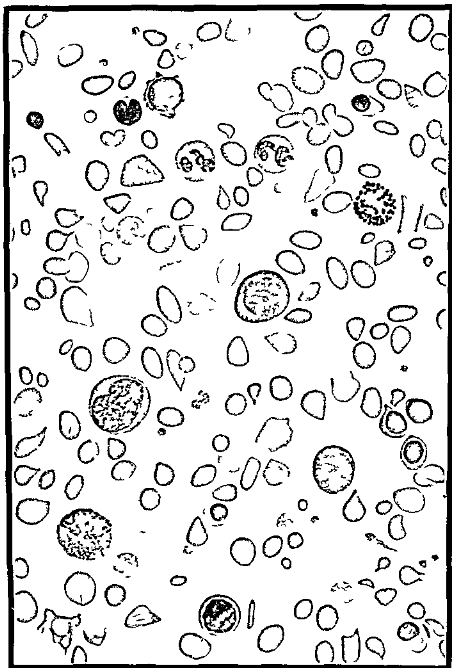
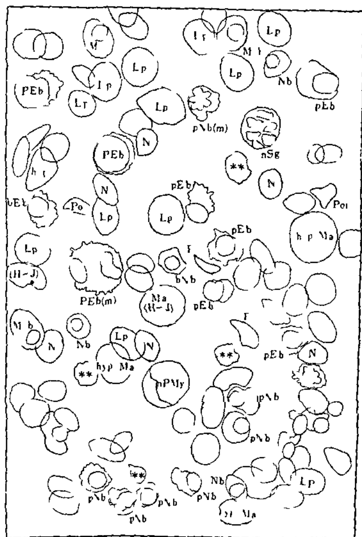


PLATE 21

Erythroblastic Anemia

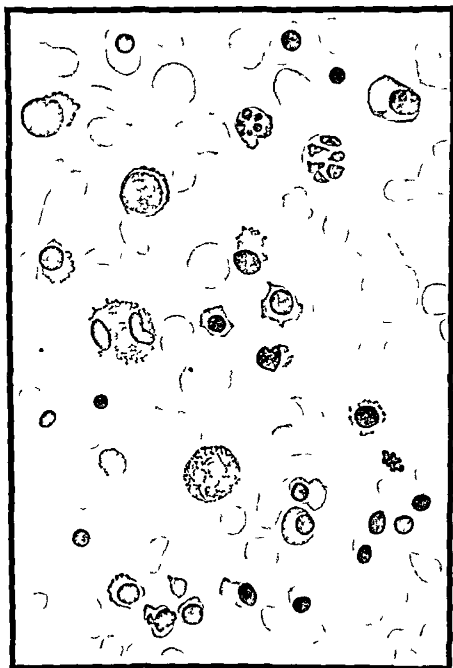
(2)



N	Normocyte
HypoMa	Hypochromic macrocyte
Lp	Leptocyte
Nb	Normoblast
Mab	Macroblast
PEb	Proerythroblast
PEb(m)	Proerythroblast (mitotic)
bEb	Basophilic erythroblast
pEb	Polychromatophilic erythroblast
H J	Howell Jolly body
**	Reticulocyte (?)
Poi	Poikilocyte
PMy	Promyelocyte
nSg	Neutrophilic segmentocyte

Plate 21 shows the blood picture of Cooley's erythroblastic anemia, in which moderately numerous, unusually large macrocytes appear in the peripheral circulation These cells are characterized by an irregular distribution of hemoglobin, probably abnormal in type leading to the formation of target cells (leptocytes).

Plate 21 Erythroblastic Anemia (2)



N	Normocyte
HypoMa	Hypochromic macrocyte
Lp	Leptocyte
Nb	Normoblast
Mab	Macroblast
PEb	Proerythroblast
PEb(m)	*Proerythroblast* (mitotic)
bEb	Basophilic erythroblast
pEb	Polychromatophilic *erythroblast*
H J	Howell Jolly body
**	Reticulocyte (?)
Poi	Poikilocyte
PMy	Promyelocyte
nSg	Neutrophilic segmen*tocyte*

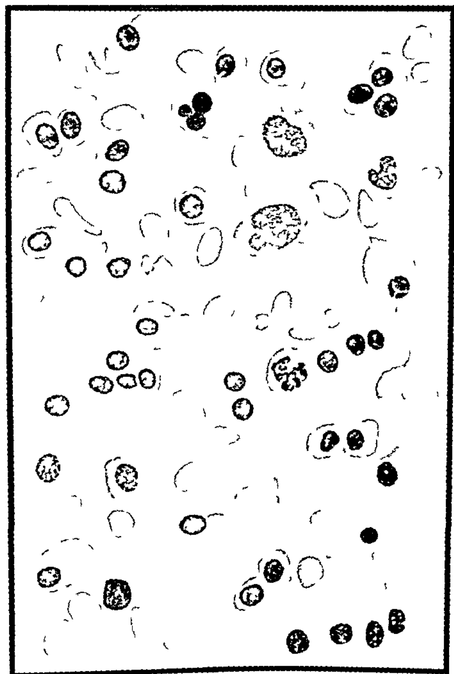
Plate 21 shows *the* blood picture of Cooley's *erythroblastic* anemia, in which moderately numerous, unusually large macrocytes appear in the peripheral circulation These cells are characterized by an irregular distribution of hemoglobin, probably abnormal in type leading to the formation of target cells (leptocytes).

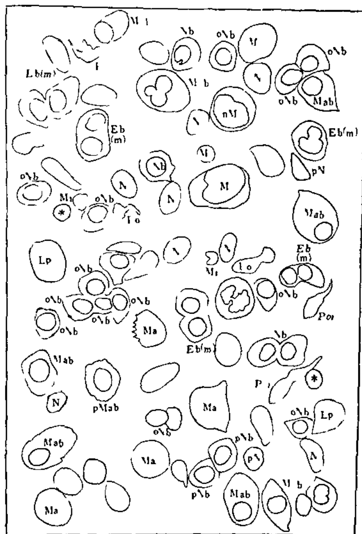
PLATE 22

Erythroblastic Anemia

(3)

Plate 22 Erythroblastic Anemia (3)



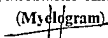


N	Normocyte
Ma	Macrocyte
Lp	Leptocyte
Mi	Microcyte
Poi	Poikilocyte
pN	Orthochromatophilic normocyte
Eb(m)	Erythroblast *(mitotic)*
Mab	Macroblast
pMab	Polychromatophilic macroblast
pNb	normoblast
*	Extruded nucleus (normoblast)
nMy	Neutrophilic myelocyte
M	*Monocyte*

Plate 22 illustrates the presence of a large number of nucleated red blood cells morphologically identical to fully matured normoblasts in the circulating blood of a young girl with erythroblastic anemia who died within a few days after this smear was made

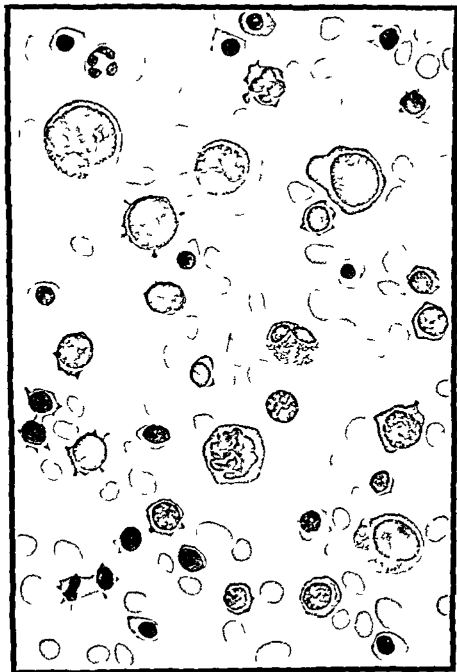
PLATE 23

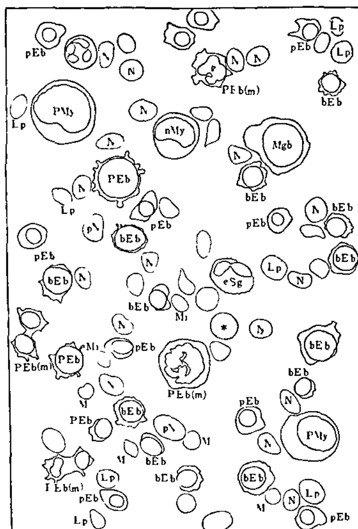
Erythroblastic Anemia



(Myelogram)

Plate 23 Erythroblastic Anemia (Myelogram)





N	Normocyte
Mi	Microcyte
pN	Polychromatophilic normocyte
Lp	Leptocyte
PEb	Proerythroblast
Mgb	Megaloblast
PEb(m)	Proerythroblast (mitotic)
bEb	Basophilic erythroblast
*	Free nucleus (normoblast)
pEb	Polychromatophilic erythroblast
PMy	Promyelocyte
nMy	Neutrophilic myelocyte
eSg	Eosinophilic segmentocyte

Plate 23 is the marrow picture of a child with erythroblastic anemia characterized by a pronounced acceleration of erythropoiesis as evidenced by the presence of numerous immature nucleated forms far outnumbering the cells of the granulocytic series

13 SICKLE CELL ANEMIA

Sickle cell anemia is a hereditary disease occurring most frequently among Negroes It is characterized by the presence of sickle shaped erythrocytes in the blood containing a type of abnormal hemoglobin (Hb S) and clinically manifested by the symptoms of hemolytic anemia rheumatoid signs leg ulcers and acute attacks of pain Since Herrick first described this disease in 1910 numerous studies chiefly on the heredity of the sickle cell trait have supported the view that only this trait or sicklemia results when the gene for sickling is heterozygous whereas sicklanemia is manifested when the gene is homozygous It follows therefore that simultaneous heterozygosity of the sickle cell gene and other genes produces a mixed clinical picture which closely resembles sickle cell anemia Among the synonyms used for this disease are drepanocytic anemia meniscocytosis sicklanemia and hemoglobin S disease Since the pathogenesis is based primarily on the abnormal globin moiety of the hemoglobin molecule Pauling (1955) called this anemia a typ of molecular disease

Clinically the symptoms are those common to all types of severe hemolytic anemia with sudden aggravations of weakness and lassitude accompanied by frequent episodes of pain in the joints and abdomen At times prostration may be so pronounced as to simulate a condition of shock Generalized lymphadeno pathy rarely splenomegaly may be found The heart is enlarged involving chiefly the left ventricle and right auricle and presents a globular configuration Sinus arrhythmia tachycardia and systolic murmur may be noted Moderate hepatomegaly spontaneous hematuria and chronic leg ulcers are frequently seen Bone changes somewhat resembling those seen in thalassemia are demonstrated on the roentgenogram Neurologic manifestations consist of drowsiness stupor hemiplegia irritability cranial nerve palsy and even convulsions

The anemia which may be severe is either normocytic or even macrocytic the size of the red cell being a function of oxygen saturation The smear preparations reveal the presence of sickle shaped erythrocytes with dimensions of 15–20 microns in length and 2–4 microns in width Polychromatophilia and reticulocytosis are almost constant When a drop of blood is kept in a reduced oxygen atmosphere the sickling of red cells can be observed to progress with the lapse of time Thrombocytosis and leukocytosis due to neutrophilia with a left shift are usual findings In observing a concentrated solution of reduced hemoglobin S under the phase contrast microscope Harris noted a characteristic tactoid formation consisting of elongated spindle shaped or rodlike particles in parallel or equidistant arrangement It was suggested that sickle cells originate as a result of this peculiar behavior The bone marrow is usually hyperplastic containing many nucleated forms and megakaryocytes

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PLATE 24

Sickle Cell Anemia
(Sicklanemia)

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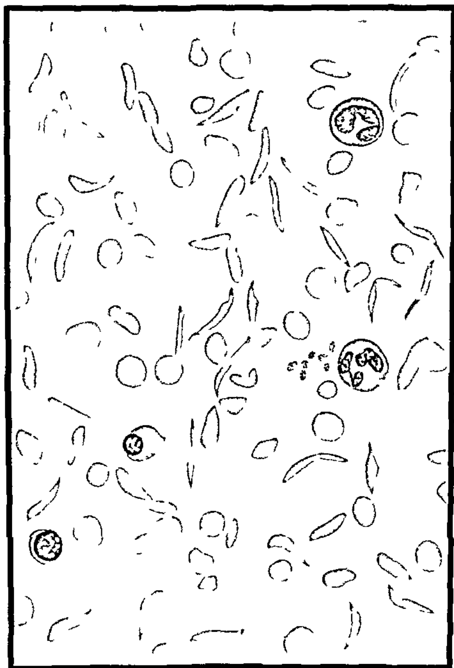
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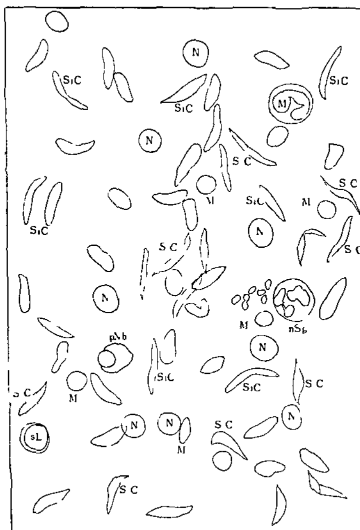
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Plate 24 Sickle Cell Anemia (Sicklanemia)





N	Normocyte
Sic	Sickle cell
Mi	Microcyte
pNb	Polychromatophilic normoblast
nSg	Neutrophilic segmentocyte
M	Monocyte
sL	Small lymphocyte

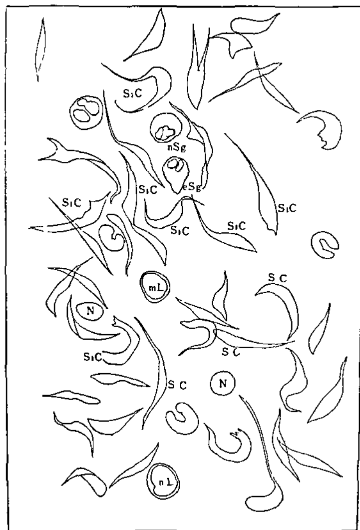
Plate 24 shows a typical picture of the peripheral blood in sickle cell anemia the charcteristic feature being the presence of drepanocytes embodying the S type of hemoglobin which represents a hereditary trait Some of the patients with sickle cell anemia (sicklanemia) have C or F types of hemoglobin in addition to Hb S and these combinations are known as S C and S F diseases (Courtesy of Dr H W Joseph)

Plate 24 Sickle Cell Anemia (Sicklanemia)



PLATE 25

Sickling Phenomenon
(Sicklemia)



N Normocyte
SiC Sickle cell
nSg Neutrophilic *segmentocyte*
eSg Eosinophilic segmentocyte
mL Mesolymphocyte

Plate 25 depicts the sickling phenomenon (sicklemia) after a patient's blood taken on a slide had stood at room temperature for 24 hours tightly sealed with Vaseline applied around the edges of a cover glass. Anoxia so produced causes nearly all of the red cells to sickle

Plate 25 Sickling Phenomenon (Sicklemia)



14 PERNICIOUS ANEMIA

Pernicious anemia so designated because of its fatal termination before the advent of liver therapy is a deficiency disease produced by the lack of intrinsic factor secreted by the gastric glands and clinically characterized by the development of *macrocytic hyperchromic anemia achylia gastrica certain gastro-intestinal* and neurologic symptoms and increased blood destruction A clear description of the disease was first given by Thomas Addison (1855) although earlier observers including Combe (1823) Andral (1823) and Marshall Hall (1837) had each recorded a similar disorder previously followed by a comprehensive account by Biermer (1872) Later additional studies on bone marrow changes hematologic peculiarities gastric pathology and spinal cord lesions by more recent observers have greatly contributed to the clear delineation of the disease The striking benefit of liver therapy in anemic dogs demonstrated by Whipple and his associates was clinically substantiated by Minot and Murphy in 1926

Despite the presence of moderately severe anemia the initial symptoms are relatively mild unless the patient develops neurologic signs early Weakness sore tongue and numbness or tingling of the limbs are generally considered to constitute the diagnostic triad Pallor and lemon yellow coloration of the skin become established when the anemia advances Glossitis and diarrhea are common and the liver and spleen may be enlarged Signs of cardiovascular derangement such as dyspnea palpitation vertigo tinnitus and edema may at times be pronounced The symptoms referrable to nerve lesions are frequent but vary according to the degree of degenerative changes of the spinal cord and peripheral nerves Fever may accompany anemia but it dissipates under liver treatment

Hematologically the most unusual finding is the presence of variable numbers of megalocytes and occasional megaloblasts in the peripheral blood The Price Jones curve reveals a typical skew with a peak in the neighborhood of 9 microns the mean corpuscular volume ranging from 110 to 130 cubic microns The mean corpuscular hemoglobin concentration is correspondingly high in proportion to the increase in red cell size In brief the blood picture in pernicious anemia is characterized by macrocytosis hyperchromia as well as anisocytosis and poikilocytosis The presence of Cabot s rings and Howell Jolly bodies may be demonstration in some instances

As a rule the number of peripheral leukocytes is decreased associated with absolute neutrophilia and relative lymphocytosis The occurrence of a few multilobulated hypersegmented and exceptionally huge neutrophilocytes sometimes called macropolycytes (Cooke) is a striking feature of the blood and their presence has often been given a diagnostic value in pernicious anemia The bone marrow hyperplasia is indicated by the proliferation of promegaloblasts and megaloblasts as well as of macropolycytes Upon the initiation of adequate dietary therapy including the use of liver extract cyanocobalamine folic acid and citrovorum factor or folinic acid the abnormalities of the blood and bone marrow are satisfactorily corrected

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PLATE 26

Pernicious Anemia

(1)

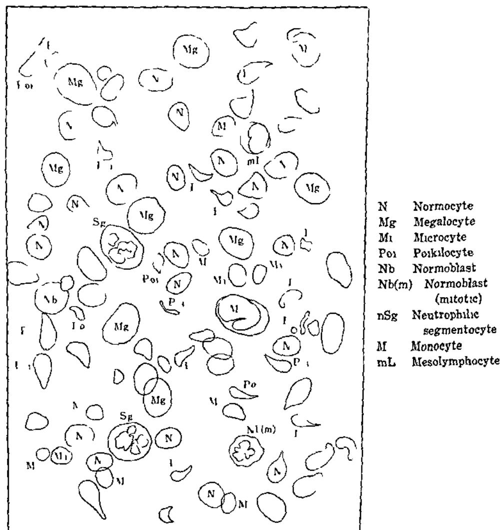
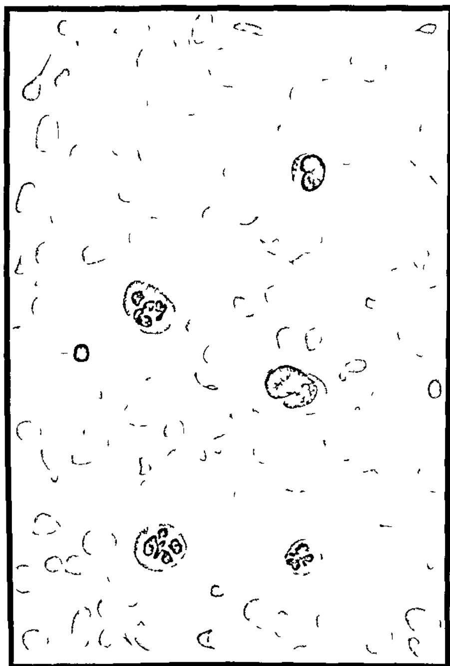


Plate 26 illustrates one phase of the peripheral blood in pernicious anemia in which the erythrocytes exhibit an extreme degree of anisocytosis due to the admixture of megalocytes normocytes microcytes and poikilocytes The hemoglobin concentration in the average red cell appears to be nearly normal and no megaloblasts are seen

Plate 26 Pernicious Anemia (1)



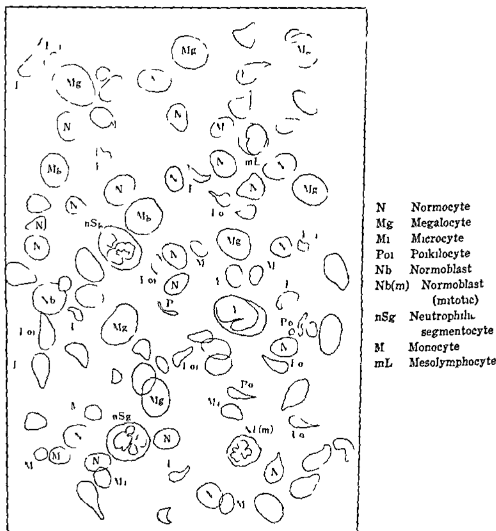


Plate 26 illustrates one phase of the peripheral blood in pernicious anemia in which the erythrocytes exhibit an extreme degree of anisocytosis due to the admixture of megalocytes, normocytes, microcytes and poikilocytes. The hemoglobin concentration in the average red cell appears to be nearly normal, and no megaloblasts are seen.

PLATE 27

Pernicious Anemia

(2)

PLATE 27

Pernicious Anemia

(2)

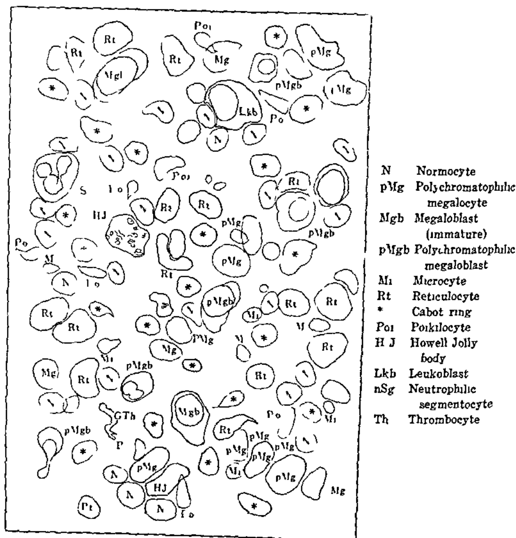


Plate 27 depicts the most typical and remarkable changes in the red cell morphology characteristic of pernicious anemia The presence of Cabot rings and Howell Jolly bodies in a number of erythrocytes of varying sizes with extreme staining abnormalities is spectacular All stages of maturation from megaloblasts to megalocytes are also represented

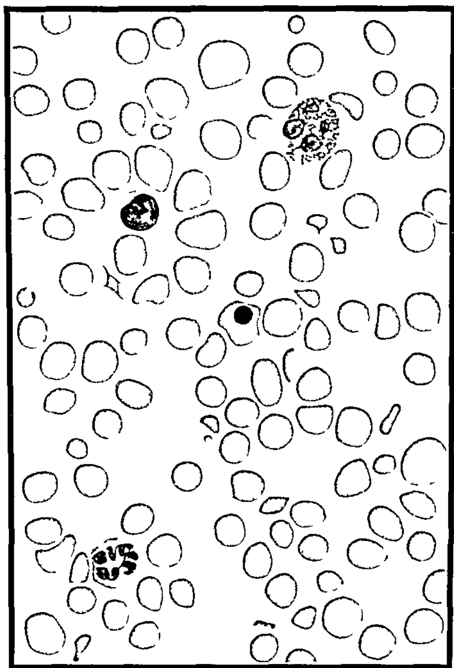
Plate 27 Pernicious Anemia (2)

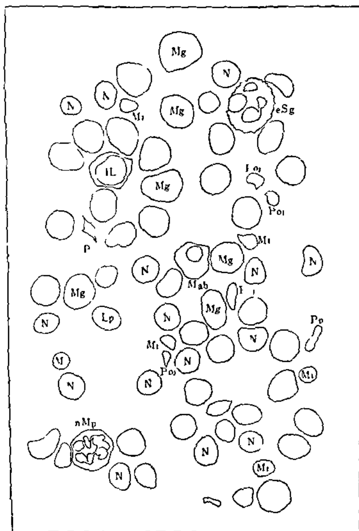


PLATE 28

Pernicious Anemia
(3)

Plate 28 Pernicious Anemia (3)





N	Normocyte
Mg	Megalocyte
Mi	Microcyte
Poi	Poikilocyte
Lp	Leptocyte
Mab	Macroblast
nMp	Neutrophilic macropolycyte
eSg	Eosinophilic segmentocyte
lL	Large lymphocyte

Plate 28 is the peripheral blood picture of a patient with pernicious anemia who developed typical achlorhydria and neurologic manifestations The most characteristic hematologic finding consists of the fairly high concentration of hemoglobin in the megalocytes The red cell count was 2 000 000 with 83 per cent hemoglobin while the white cell count was 4 100 The nuclei of both neutrophilic and eosinophilic granulocytes show a tendency to hypersegmentation

Plate 28 Pernicious Anemia (3)

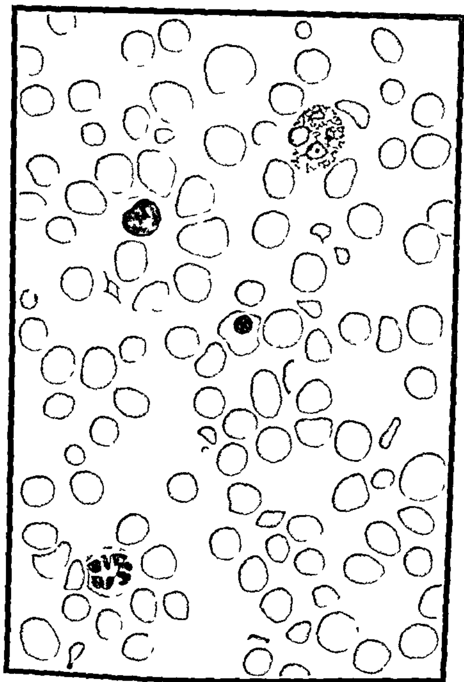
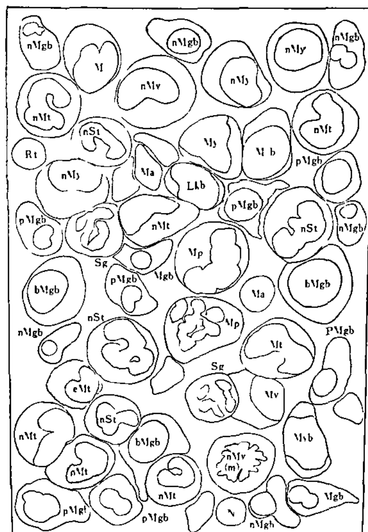


PLATE 29

Pernicious Anemia

(4)



N	Normocyte
Ma	Macrocyte
nMgb	Orthochromatic megaloblast
pMgb	Polychromatophilic megaloblast
bMgb	Basophilic megaloblast
Rt	Reticulocyte
Myb	Myeloblast
Lkb	Leukoblast
nMy	Neutrophilic myelocyte
nMy(m)	Neutrophilic myelocyte (mitotic)
nMt	Neutrophilic metamyelocyte
nSt	Neutrophilic stab cell
nSg	Neutrophilic segmentocyte
Mp	Macropolycyte
eMt	Eosinophilic metamyelocyte
M	Monocyte

Plate 29 demonstrates the myelogram in pernicious anemia as seen on a touch preparation made from the patient's bone marrow material. The development of neutrophilic macropolycytes (polykaryocytes) as well as the maturation of megaloblasts into megalocytes can be traced. (Courtesy of Dr. O. P. Jones.)

Plate 29 Pernicious Anemia (Myelogram)



15 IDIOPATHIC STEATORRHEA (SPRUE)

Idiopathic steatorrhea or sprue is a chronic wasting disease clinically characterized by glossitis diarrhea with the passage of bulky frothy stools containing an abundance of undigested fat and by the development of macrocytic anemia This disorder possibly including both tropical and nontropical forms was first identified by Vincent Katalear in 1669 subsequently other names such as indische sprew psilosis and aphthae tropicae were used by older writers Later Gee in 1888 and Herter in 1908 described this disease under the name of coeliac affection occurring mostly in infants and young children now called coeliac disease presenting all the characteristics of idiopathic steatorrhea While the etiology of sprue has not been conclusively elucidated evidence indicates its relation to serious metabolic defects particularly in the utilization of fats and minerals

The onset of this disease is insidious with indefinite symptoms consisting chiefly of mild digestive disturbances and nervous irritability The failure to gain weight accompanied by advancing weakness is the earliest definite sign of illness to be noticed *Small aphthous eruptions may appear on the tongue* which become red and sensitive to the touch of food Abdominal distention with flatulence may be remarkable and dyspepsia and diarrhea are constant in later stages The stools are soft mushy and watery in consistency voluminous and light colored containing an excess of fat and unsaturated fatty acids Upon roentgenographic examination using barium meal the entire outline of the intestinal tract is found to be coarse and presents a lead pipe or wax model appearance (moulage sign) The small intestine may show abnormal segmentation due to the irregular peristalsis attributable to nutritional deficiency or disordered motor function

Hematologically the blood and bone marrow in idiopathic steatorrhea resemble those seen in typical pernicious anemia in all essential features

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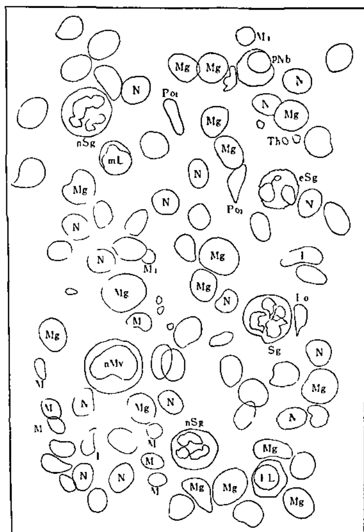
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PLATE 30

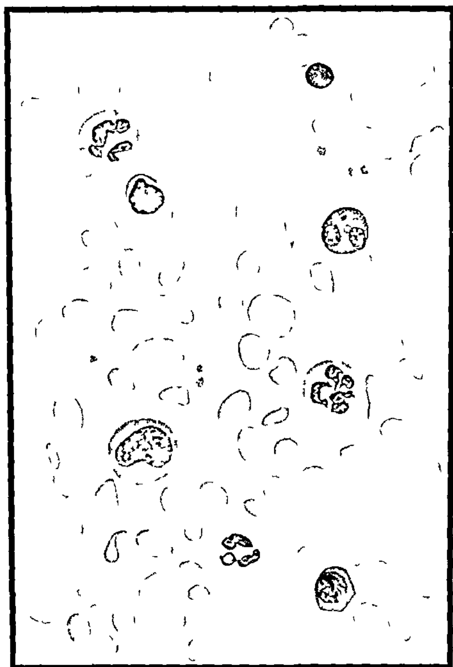
Sprue



N Normocyte
Mg Megalocyte
Mi Microcyte
Poi Poikilocyte
pNb Polychromatophili normoblast
nMy Neutrophilic myelocyte
nSg Neutrophilic segmentocyte
eSg Eosinophilic segmentocyte
mL Mesolymphocyte
Th Thrombocyte

Plate 30 is the peripheral blood picture in tropical sprue which in many respects resembles that of pernicious anemia The noteworthy features are the anisocytosis and poikilocytosis together with the presence of a few polychromatophilic normoblasts and hypersegmented neutrophilic granulocytes

Plate 30 Sprue



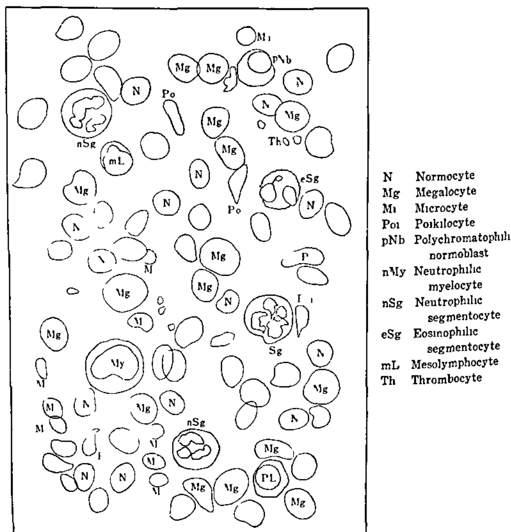


Plate 30 is the peripheral blood picture in tropical sprue which in many respects resembles that of pernicious anemia The noteworthy features are the anisocytosis and poikilocytosis together with the presence of a few polychromatophilic normoblasts and hypersegmented neutrophilic granulocytes

16 HEMOLYTIC ANEMIAS

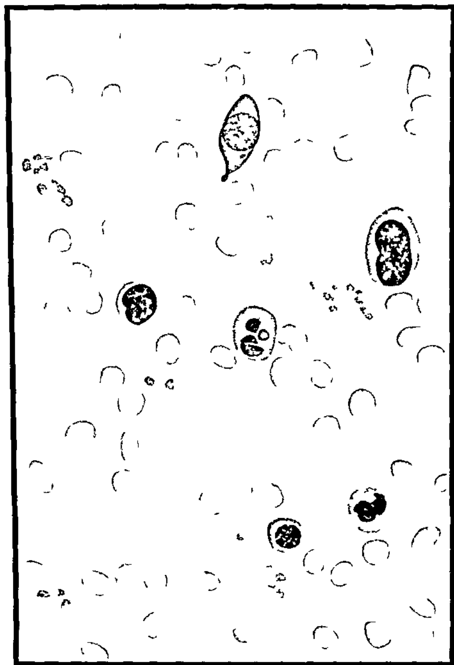
Hemolytic anemias comprise a great variety of anemic states whether primary or secondary having in common abnormally increased blood destruction as their most characteristic features Since the etiologic factors involved in producing excessive hemolysis are so numerous it is extremely difficult to evolve a comprehensive classification of these anemias for complete understanding of the underlying mechanisms As hemolysis represents a result of interaction between the red corpuscles and their surrounding medium the fault may lie in either of these factors although it is also conceivable that both may at times be abnormal Wintrobe (1956) has suggested that hemolytic anemias can be grouped according to whether the defect is internal or intracorpuscular thus leading to accelerated destruction or is due to the action of extracorpuscular substances having hemolysinic properties As a rule the intracorpuscular mechanism is predominantly involved in giving rise to the hereditary or familial form while the extracorpuscular agents are responsible for producing the acquired or secondary form of the disease Irrespective of the cause however the symptoms as well as the course of the disease seem to be influenced by the extent and rapidity of the hemolytic process occurring in the body The blood pictures of acute hemolytic anemia and of congenital hemolytic jaundice reproduced in the following plates illustrate the secondary and primary forms respectively

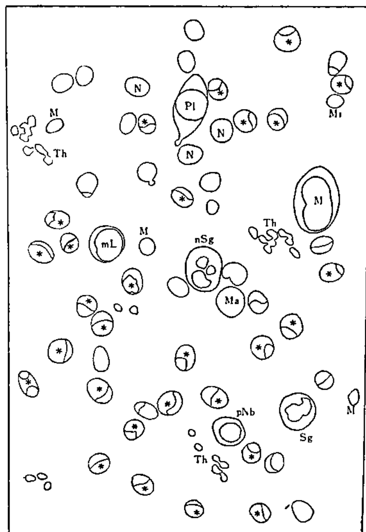
(1) **Acute hemolytic anemia** is a severe type of anemia arising from various causes and characterized by a rapidly progressing course but usually responding well to such simple measures as blood transfusion and symptomatic medication Since Lederer described the first case under this designation in 1925 and in view of similar cases subsequently reported by other observer this condition is generally regarded as being distinct from congenital familial jaundice in acute crisis

During the acute stage the peripheral blood is characterized by the rapid development of anemia the red blood cells showing microcytosis anisocytosis and hypochromia of extreme degrees Morphologically the distribution of hemoglobin within the cell is found to be most unusual in that the pigment tends to be irregularly deposited most frequently aggregated to one side of the cell so that the other side appears to be completely empty This bizarre deposition of hemoglobin makes the cell present a bucket like form (bucket cell) giving an impression of increased fragility quite analogous to the spherocytes in congenital hemolytic icterus

(2) **Congenital hemolytic jaundice** is a type of hemolytic anemia characterized by excessive intravascular blood destruction resulting from the action of hemolysins present in the plasma generally considered to have been transmitted genetically While the classic form of the disease first described by Minkowski and later by Chauffard is essentially a chronic condition Hayem and afterward Widal and co workers called attention to the existence of another type which is acquired and often acute in clinical manifestations That such is the case has been demonstrated by Dameshek and Schwartz who confirmed clinically as well as experimentally the presence of abnormal hemolysins in the plasma capable of producing spherocytosis It appears likely therefore that the factors determining the clinical type or course of the disease seem to depend largely on the concentration of such antibodies in the plasma Numerous synonyms for this

Plate 31 Acute Hemolytic Anemia





N	Normocyte
*	Bucket cell
Ma	Macrocyte
Mi	Microcyte
pNb	Polychromatophilic normoblast
nSg	Neutrophilic segmentocyte
M	Monocyte
mL	Mesolymphocyte
Pl	Plasmacyte
Th	Thrombocyte

Plate 31 is the peripheral blood picture in a young child with acute hemolytic anemia (Lederer) The most unusual feature of this blood is the presence of a large number of microcytes in which the hemoglobin is aggregated to one side of the cell leaving a mere membranous outline on the opposite side (bucket cells)

Plate 31 Acute Hemolytic Anemia

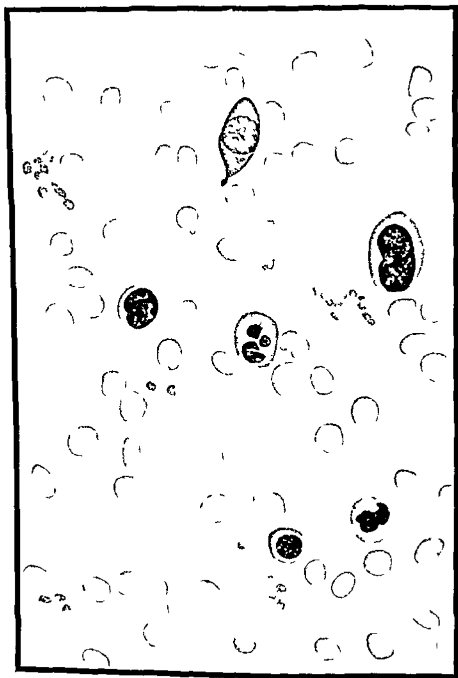
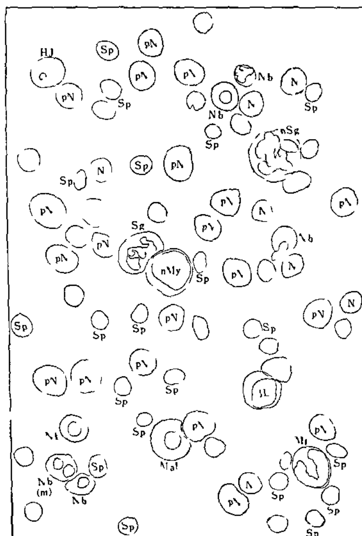


PLATE 32

Congenital Hemolytic Jaundice

(1)



N	Normocyte
pN	Polychromatophilic normocyte
Sp	Spherocyte
Nb	Normoblast
Nb(m)	Normoblast (mitotic)
H J	Howell Jolly body
Mab	Macroblast
nMy	Neutrophilic myelocyte
nMt	Neutrophilic metamyelocyte
nSg	Neotrophilic segmentocyte
lL	Large lymphocyte

Plate 32 depicts the typical blood picture in congenital (familial) hemolytic jaundice in a 29 year old female patient under treatment at Mayo Clinic The white cell count was 17 000 while the red cells numbered only 950 000 many of which were large and polychromatophilic The presence of many microcytic spherocytes is a feature of diagnostic importance

Plate 32 Congenital Hemolytic Jaundice (1)

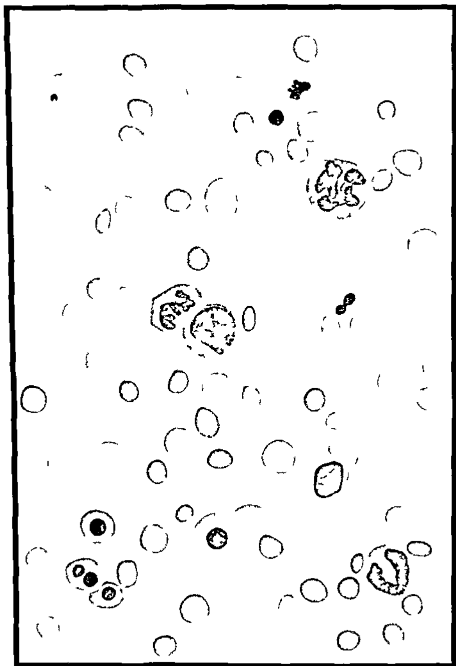


PLATE 33

Congenital Hemolytic Jaundice

(2)

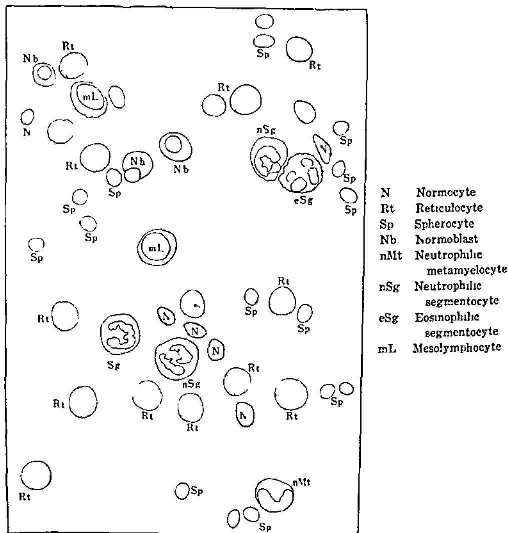


Plate 33 demonstrates the picture obtained after the same blood sample shown in the preceding plate had been supravitally treated with brilliant cresyl blue solution and counterstained by Wright's method. Nearly 50 per cent of the red blood cells are found to contain the granulofilamentous substances (reticulocytes).

Plate 33 Congenital Hemolytic Jaundice (2)

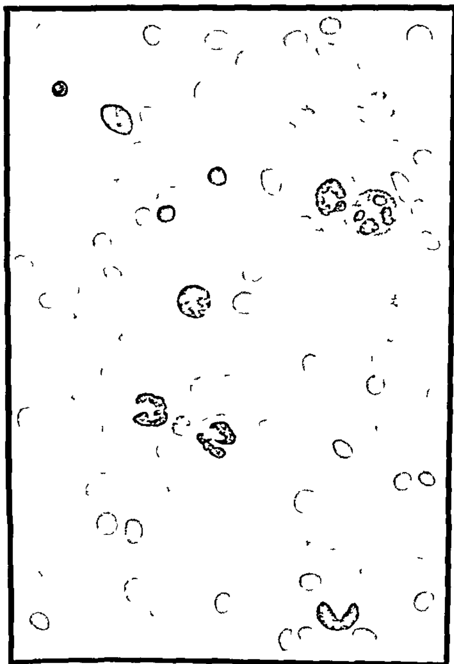


PLATE 34

Congenital Hemolytic Jaundice

(3)

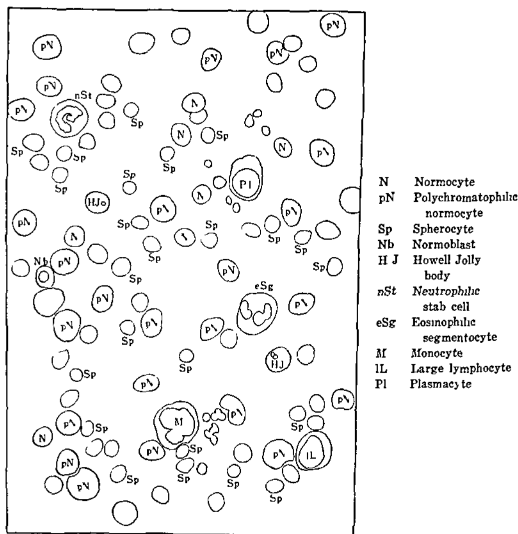
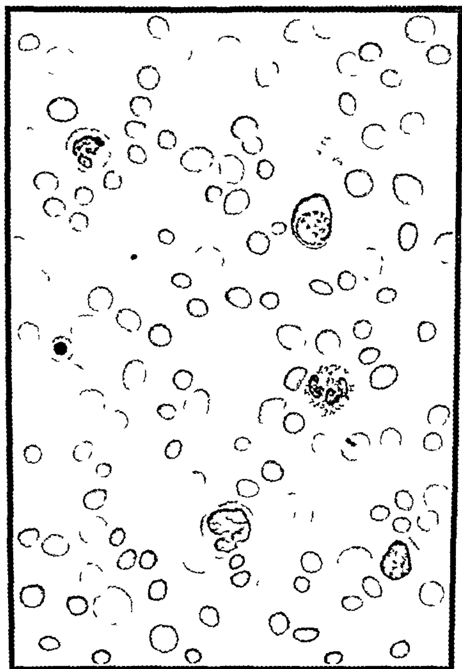


Plate 34 is the blood picture seen after splenectomy in the same patient whose *preoperative blood pictures are shown in the two preceding plates It is note*worthy that both spherocytosis and reticulocytosis persist even though the patient showed a marked improvement in clinical manifestations of the disease The percentage of the nucleated red cells however was significantly reduced after the operation

Plate 34 Congenital Hemolytic Jaundice (3)



17 IDIOPATHIC THROMBOCYTOPENIC PURPURA

Idiopathic thrombocytopenic purpura (ITP) is a hemorrhagic disease with constitutional manifestations primarily due to the reduction of blood platelets and clinically manifested by such symptoms as petechiae ecchymoses and even suffusions or suggillations in the skin and mucous membranes as well as bleeding *into various organs and tissues* *The disorder was first described by Werlhof* in 1735 and was known as Werlhof's disease or morbus maculosus werlhofi Since then numerous synonyms have been used thrombocytolytic purpura hemogenic syndrome and essential or primary thrombocytopenic purpura The most important feature in the etiology of this disease is the existence or development of an antiplatelet immune body exerting a destructive action on the platelets and megakaryocytes Such an antibody has been found in the spleen extract of patients with this disease by Troland and Lee who called it thrombocytopen Kawano produced a similar substance experimentally by immunizing the animals with human platelets

The symptoms most commonly encountered consist of easy bruising and purpuric lesions which may coalesce to form large areas of cutaneous and subcutaneous hemorrhage Hematomas and visceral bleeding may occur Nasal and gingival hemorrhages are also common Bleeding from the mucous membrane of the urogenital and alimentary tracts are sometimes seen while intracranial hemorrhage may cause grave symptoms

The blood is characterized by an extreme decrease of circulating platelets or even their complete absence and when present a few of these elements may assume huge dimensions (giant platelets) The leukocyte picture is usually normal but may present a leukemoid reaction Anemia which is normocytic as a rule is proportional only to the extent of blood loss Bleeding time is markedly prolonged while coagulation time is either normal or slightly delayed Clot retraction is poor and may be practically absent Capillary fragility test as determined by either positive or negative method as well as venom skin test is markedly positive The bone marrow presents a remarkable megakaryocytic hyperplasia and the morphologic and functional abnormalities of the thrombopoietic apparatus are conspicuous in acute but less so in chronic cases Splenectomy is indicated in the latter instances

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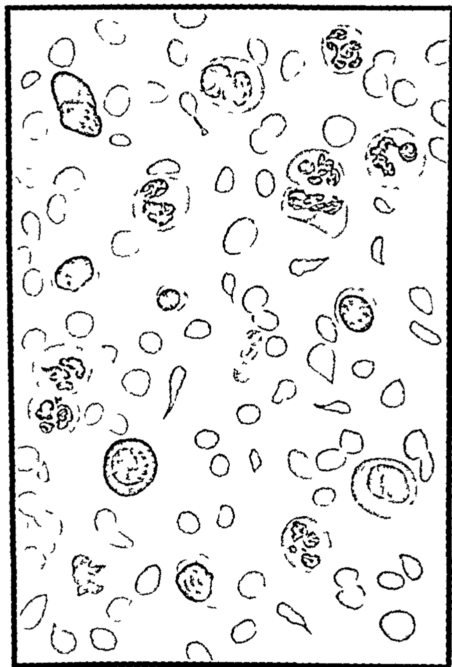
PLATE 35

Idiopathic Thrombocytopenic Purpura

N	Normocyte
Mi	Microcyte
pN	Polychromatophilic normocyte
Poi	Poikilocyte
pNb	Polychromatophilic normocyte
nMy	Neutrophilic myelocyte
nMt	Neutrophilic metamyelocyte
nSg	Neutrophilic segmentocyte
M	Monocyte
lL	Large lymphocyte

Plate 35 illustrates the blood picture of a female child 2.5 years old with idiopathic thrombocytopenic purpura. The platelet count was only 50 000 but many giant thrombocytes were present. Severe purpura accompanied by obstinate gingival bleeding and epistaxis was controlled only after splenectomy.

Plate 35 Idiopathic Thrombocytopenic Purpura



18 ERYTHREMIC MYELOSIS

Frythremic myelo is i t is ubacute or chronic in course is a blood dis order in which the erythropoietic tissue exhibits a proliferative change almost resembling that of a neopl tic proce s while the peripheral blood shows severe anemia without reticulocytosis The disease is clinically characterized by re mittent fever marked plenomegaly moderate enlargement of the liver and fatal termination often associated with hemorrhagic tendencies The acute type of this disease is usually called Di Guglielmo s disease and a chronic form was described by Heilmeyer and Schoner (1941) Komiya (1953) prefers to consider the chronic type as being either subacute or subchronic the truly chronic type being polycythemia vera However Schwartz and Critchlow (1952) after care fully reviewing all the cases reported in the literature up to the time of their writing concluded that the acute type of Di Guglielmo and the chronic form of Heilmeyer and Schoner both being characterized by refractory anemia should be collectively called erythremic myelosis which is quite different from poly cythemia vera This condition can be distinguished from myelosclero is or leukoerythroblastosis by the absence of any evidence of fibrosis of the marrow

In acute erythremic myelosis the rapidly developing anemia may assume a refractory nature accompanied by fever and progressive enlargement of the liver and spleen Death usually occurs within a few months after episodes of bleeding symptoms The blood picture is characterized by the presence of numerous pronormoblasts and normoblasts a tendency to leukopenia and thrombo cytopenia At autopsy the organs are found to be infiltrated with histiocytes and immature erythroid cells with little evidence of maturation

The duration of the chronic disease is about two years the symptoms being somewhat similar to those of the acute form only less in degree but the nucleated red cells appearing in the peripheral blood consist mostly of more mature normoblasts Hemorrhagic manifestations are practically lacking The bone marrow is hyperplastic and evidences of extramedullary hematopoiesis may be demonstrated

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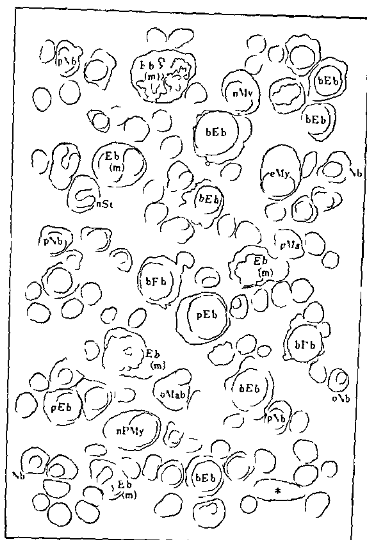
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PLATE 36

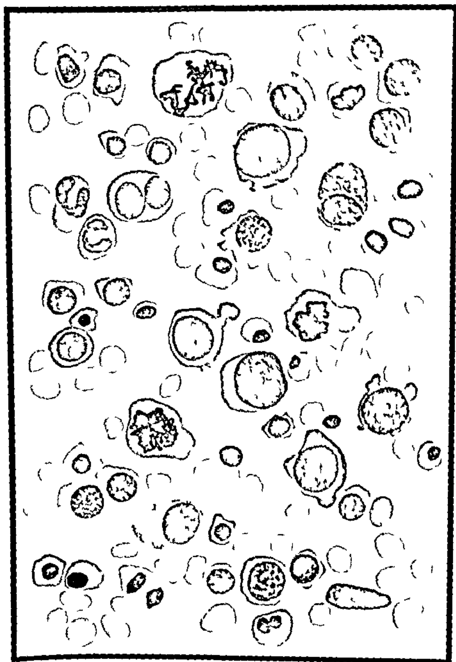
Erythremic Myelosis

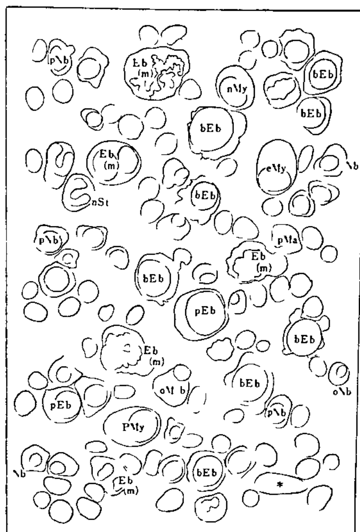


pNb	Polychromatophilic normoblast
oNb	Orthochromatic normoblast
bEb	Basophilic erythroblast
pEb	Polychromatophilic erythroblast
Eb(m)	Erythroblast (mitotic)
pMa	Polychromatophilic macrocyte
oMab	Orthochromatic macroblast
eMy	Eosinophilic myelocyte
nMy	Neutrophilic myelocyte
nPMy	Neutrophilic promyelocyte
nSt	Neutrophilic stab cell
*	Unidentified

Plate 36 represents the myelogram in erythremic myelosis as seen on a smear of the puncture material from Prof Komiya's patient The presence of many nucleated red cells representing all stages of development some being in active mitoses offers ample evidence of an accelerated erythropoiesis A low red cell count of 2 020 000 with 53 per cent hemolobin 17 per cent reticulocytes and a platelet count of 18 900 are also significant

Plate 36 Erythremic Myelosis



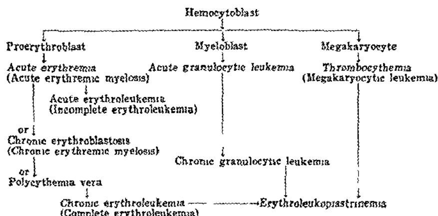


pNb	Polychromatophilic normoblast
oNb	Orthochromatic normoblast
bEb	Basophilic erythroblast
pEb	Polychromatophilic erythroblast
Eb m)	Erythroblast (mitotic)
pMa	Polychromatophilic macrocyte
oMab	Orthochromatic macroblast
eMy	Eosinophilic myelocyte
nMy	Neutrophilic myelocyte
nPMy	Neutrophilic promyelocyte
nSt	Neutrophilic stab cell
*	Unidentified

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19 ERYTHROLEUKEMIA

The term erythroleukemia was first applied by Meyers in 1928 to a blood disorder characterized by a simultaneous or mixed hyperplasia of leukoblastic and erythroblastic tissues often associated with thrombocythemia The differentiation of erythroleukemia from such closely related conditions as leukoerythroblastosis or erythremic myelosis is often exceedingly difficult Since the proliferative changes do not necessarily occur in a synchronistically parallel manner the hematologic as well as clinical picture may differ from time to time This may explain why so many synonyms have appeared in the literature such as panmyelosis myelogeneous polycythemia hypertrophic panmyelopathy and subleukemic erythremia Di Guglielmo (1946) proposed the name of erythroleukopiastrinemia for this condition in which there is definite evidence of thrombocytic hyperplasia The relationship assumed to be existing between this and kindred conditions may be represented by the following scheme

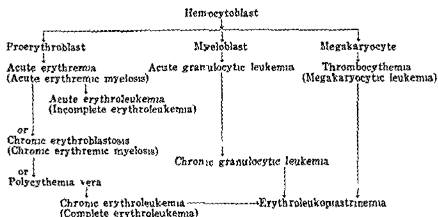


In the incomplete type of erythroleukemia with thrombocytopenia the course of the disease is usually acute associated with severe anemia moderate enlargement of the liver and spleen myeloblastemia and erythroblastemia and accompanied by hemorrhagic manifestations The complete type is characterized by its close resemblance to polycythemia vera with definite evidences of leukocytosis or to chronic myelocytic leukemia with associated polycythemia

Hematologically the acute form of the disease is marked by the presence of severe anemia with greatly diminished red cell count and hemoglobin content Leukopenia and thrombocytopenia are frequently found The cellular immaturity in both the erythroid and myeloid series is evident in the peripheral blood as well as in the bone marrow One of the most peculiar findings is the multiplication of large atypical erythroblasts containing two or more nuclei particularly in the bone marrow which have been called by such names as megaloblastoid cells or paramegaloblasts

19 ERYTHROLEUKEMIA

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PLATE 37

Erythroleukemia

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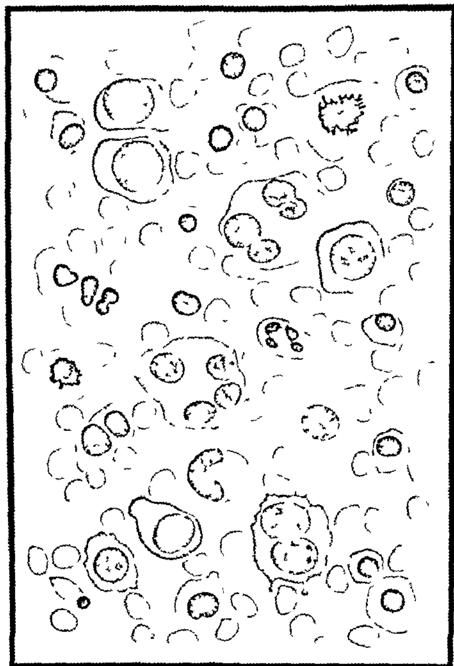
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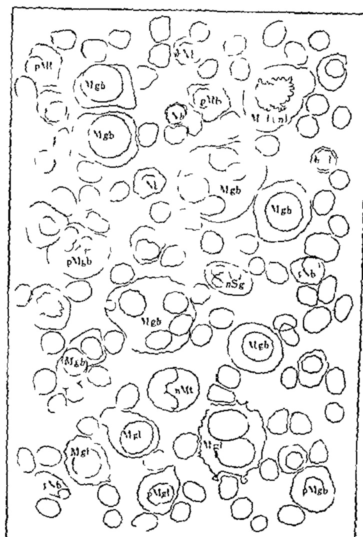
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Plate 37 Erythroleukemia

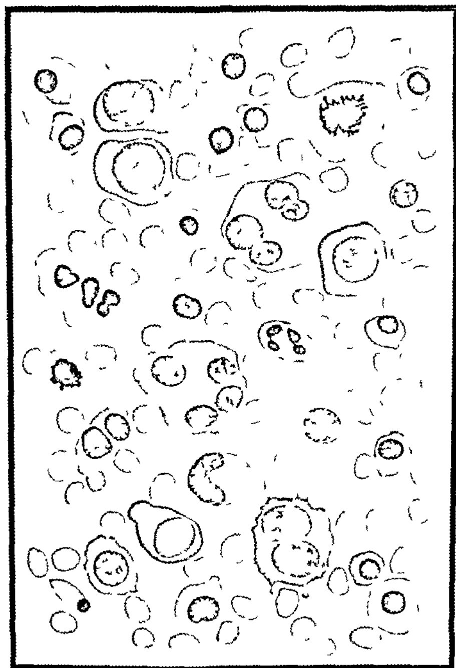


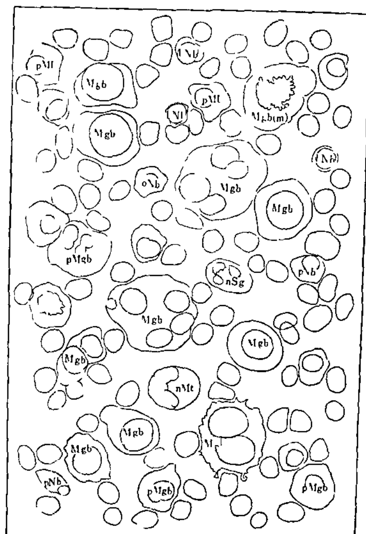


bNb	Basophilic normoblast
pNb	*Polychromatophilic* normoblast
oNb	Orthochromatic normoblast
pMb	Polychromatophilic macroblast
Mgb	Megaloblastoid cell
pMgb	Polychromatophilic megaloblast
nMt	Neutrophilic metamyelocyte
nSg	Neutrophilic segmentocyte
Mgb m)	Megaloblastoid cell (mitotic)

Plate 37 delineates the *bone* marrow *picture* of a 31 year old female patient with erythroleukemia *Blood* examination at the *time the puncture material* was obtained *revealed* 1 450 000 red cells 32 per cent hemoglobin but *only* 4 per cent reticulocytes and 27 750 platelets There were many *nucleated* red cells of which the majority were large *megaloblastoid* (Courtesy of *Prof* E Komiya)

Plate 37 Erythroleukemia





bNb	Basophilic normoblast
pNb	Polychromatophilic normoblast
oNb	Orthochromatic normoblast
pMb	Polychromatophilic macroblast
Mgb	Megaloblastoid cell
pMgb	Polychromatophilic megaloblast
nMt	Neutrophilic metamyelocyte
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Plate 37 delineates the bone marrow picture of a 31 year old female patient with erythroleukemia Blood examination at the time the puncture material was obtained revealed 1 450 000 red cells 32 per cent hemoglobin but only 4 per cent reticulocytes and 27 750 platelets There were many nucleated red cells of which the majority were large megaloblastoid (Courtesy of Prof E Komiya)

20 POLYCYTHEMIA

Polycythemia is a term generally applied to any hematologic condition characterized by an abnormal multiplication of circulating erythrocytes resulting in a high cell count elevated hemoglobin content and increased cell mass The condition may be relative transient or absolute depending on the nature of the underlying cause in each instance Relative polycythemia represents a state of unbalance between the intake and loss of body fluids in which the *total blood volume is reduced in consequence of decreased plasma volume When the red cells are shunted into the circulation from the spleen or other reservoirs in response to some stimulus the result is a transient polycythemia Both of* these types may best be *designated as symptomatic erythrocytosis* whereas polycythemia of idiopathic or unknown etiology usually accompanied by evidence of bone marrow hyperplasia is considered to be absolute To this disease which has been known for many years by the classic name of polycythemia vera the name of erythremia is now being applied comparable to the customary use of the term leukemia

1 **Erythrocytosis** occurs during the neonatal period and it may be regarded as a physiologic process associated with the transition from intrauterine to extrauterine life or it may even represent an aftermath of fetal polycythemia Symptomatic erythrocytosis often arises during the course of pulmonary diseases Ayerza s syndrome cardiorenal disorders congenital heart disease as well as under various conditions created by chemical or physical stimulations Stated in general terms erythrocytosis of secondary nature is most likely to result from a long continued defective oxygenation *of arterial blood circulatory and renal abnormalities and disturbances in the physiologic function of the red cells due particularly to altered* hemoglobin synthesis

2 ***Erythremia** or **polycythemia vera** is a chronic often familial disease of unknown etiology characterized* by a permanent increase in the number and mass of circulating erythrocytes associated with definite signs of bone marrow activity Many synonyms have been used for this disease the most common ones being splenomegalic polycythemia Osler Vaquez s disease polycythemia rubra myelopathic polycythemia erythrocytosis megalosplenica and cryptogenic polycythemia The first report of polycythemia vera was made by Vaquez (1892) followed by a study of Turk (1902) who found a leukocytosis in this disease together with the presence of some immature forms of both red and white cells The most comprehensive description of the disease was given by Osler (1903 1904)

The initial symptoms include unusually red color of the skin headache dizziness tinnitus dyspnea *weakness hemorrhages and splenomegaly In polycythemia complicated by hypertension known as Gaisbock s syndrome no splenic enlargement occurs Duodenal* ulcers may be found in association with *hemorrhages from esophageal varices or from gastrointestinal mucosa Thrombosis* is frequently encountered in the portal vein and in mesenteric vessels Hepatomegaly associated with cirrhotic changes may occur which is referred to as Mosse syndrome The neuromuscular manifestations are headache lassitude vertigo insomnia and numbness and tingling of the fingers Vision is often interfered with and the eye ground shows the retina to be deeply colored with generalized engorgement The involvement of the cerebral vessels may lead

PLATE 38

Polycythemia Vera

to paralyses of varying degrees

The most constant feature of the blood picture is naturally the extremely high values in the number and volume of red cells the highest figures ever reported being 92 per cent of packed cells with a count of 10 370 000 (Zadek 1927) The mean corpuscular volume may occasionally be low but the hemoglobin content is usually high The morphology of individual red cells is not abnormal although the presence of a few normoblasts may be noted Leukocytosis up to the highest recorded number of 58 000 may be seen and some immature forms such as myelocytes and metamyelocytes but no myeloblasts may be found There is also apt to be a concomitant thrombocytosis in this disease the highest value of 6 000 000 having been obtained by some observers The fragility test shows a lengthened span and some evidence of increased blood destruction has been demonstrated The bone marrow often shows an extreme degree of hyperplasia involving in most cases not only the normoblastic elements but also the myelocytic and megakaryocytic constituents as well

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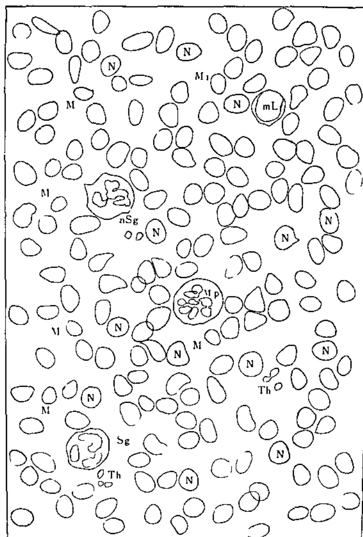
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PLATE 38

Polycythemia Vera



N	Normocyte
Mi	Microcyte
nSg	Neutrophilic segmentocyte
Mp	Polykaryocyte
mL	Mesolymphocyte
Th	Thrombocyte

Plate 38 depicts the peripheral blood picture of polycythemia vera (Osler Vaquez) in a 49 year old female patient The red cell count was 6 480 000 th hemoglobin content 18 8 Gm per cent and the packed cell volume 61 per cent The morphology of the erythrocytes suggests a tendency to microcytosis althoug the majority are nearly normal in other respects

Plate 38 Polycythemia Vera

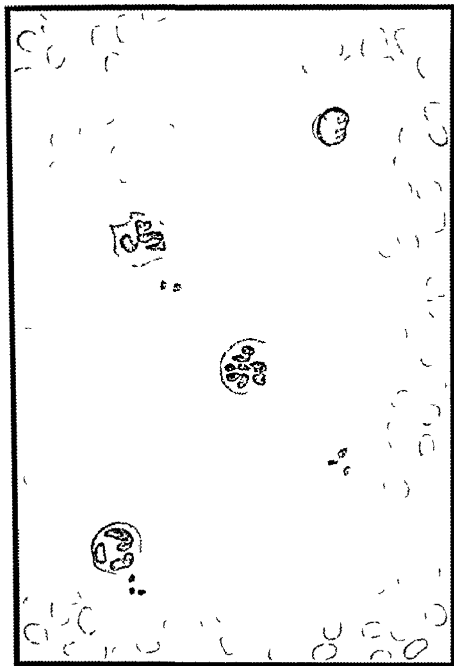
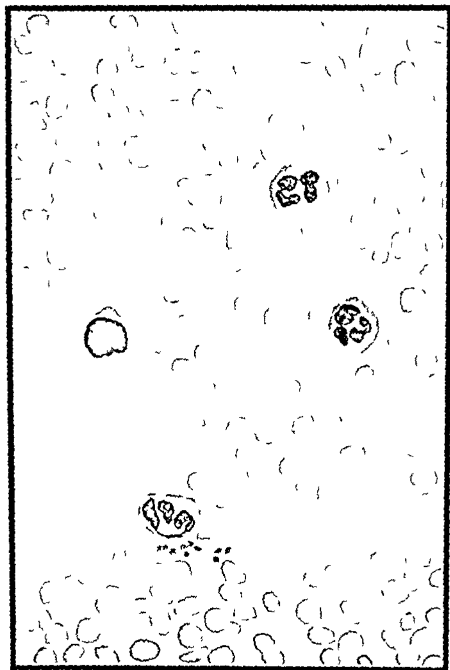
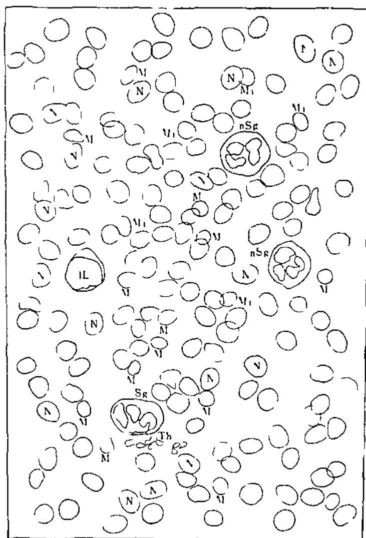


PLATE 39

Symptomatic Polycythemia

Plate 39 Symptomatic Polycythemia

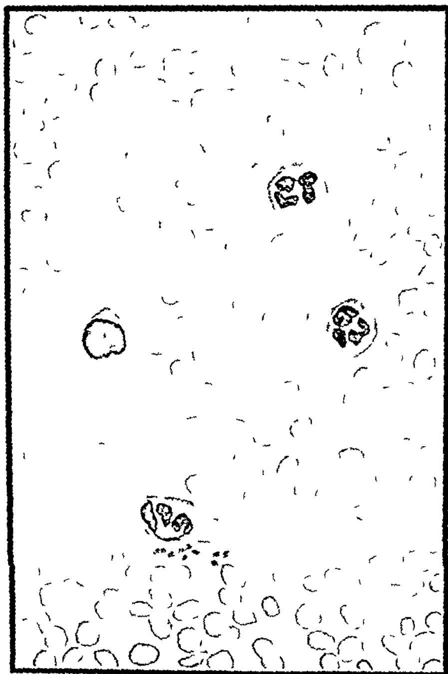




N	Normocyte
Mi	Microcyte
nSg	Neutrophilic segmentocyte
IL	Large lymphocyte
Th	Thrombocyte

Plate 39 is an instance of symptomatic polycythemia seen in a male child 5 years of age with tetralogy of Fallot The red cells are morphologically normal although there is a suggestion of microcytosis and hypochromia

Plate 39 Symptomatic Polycythemia



21 ACUTE LEUKEMIA

Although the distinction between the chronic and acute forms of leukemia is primarily based on clinical grounds it is possible to differentiate the two by demonstrating the cytologic characteristics of each type Hematologically the diagnosis of acute leukemia can readily be made when the predominating leukemic cells are chiefly of the most immature form stem cells or hemocytoblasts which exhibit very little tendency to further differentiation Because of this characteristic acute leukemia may be called stem cell leukemia or hemocytoblastic leukemia The first case of this disease was reported by Friedreich in 1857 while Ebstein (1889) gave an adequate clinical description According to the direction in which the primitive leukemic cell shows any tendency to differentiate as judged by the presence of even a small number of specific leukocytes the condition may be designated as acute lymphatic or acute myelogenous leukemia *Precise and accurate diagnosis can be made by cytologic examination of the bone marrow and other hemopoietic tissues*

The early symptoms of acute leukemia as noted by Warren (1929) are sore throat with enlarged tonsils ulcerative stomatitis and upper respiratory infection Frequently repeated hemorrhages from the nose and gums purpuric eruptions and moderate lymphadenopathy are common Fever headache and general malaise may appear suddenly with resulting prostration Splenomegaly is not usually demonstrated clinically although some enlargement occurs in nearly all cases

The anemia accompanying acute leukemia may be moderate at first but *progresses rapidly to a remarkable degree* Thrombocytopenia *is almost constantly present The leukocyte count may or may not show a great increase* at the outset but the presence of hemocytoblasts in varying numbers can be confirmed by careful observation of peripheral blood smears The bone marrow fluid aspirated by punctures is usually full of primitive cells showing evidence of excessive proliferation and accounting for 90–95 per cent of all nucleated elements These immature cells escape into the circulation in gradually or rapidly increasing numbers so that the terminal stage of the disease shows a picture of complete hemocytoblastemia in the peripheral blood

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PLATE 40

Acute Leukemia

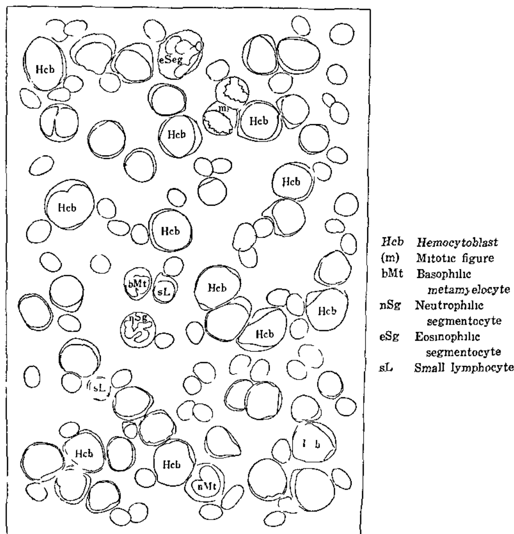
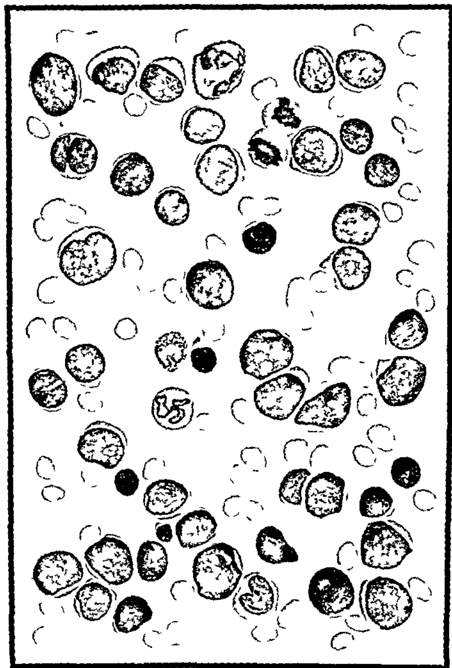
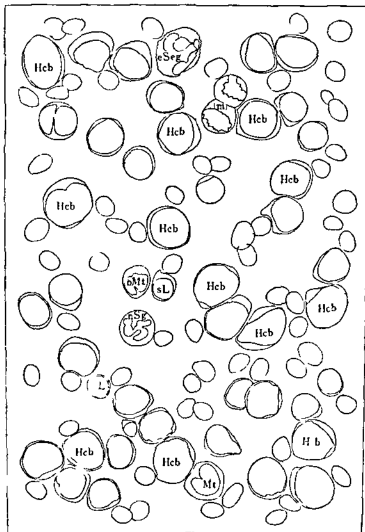


Plate 40 is the blood picture in a case of acute hemocytoblastic leukemia in a five year old female child The presence of numerous undifferentiated cells is characteristic

Plate 40 Acute Leukemia





Hcb	Hemocytoblast
(m)	Mitotic figure
bMt	Basophilic metamyelocyte
nSg	Neutrophilic segmentocyte
eSg	Eosinophilic segmentocyte
sL	Small lymphocyte

Plate 40 is the blood picture in a case of acute hemocytoblastic leukemia in a five year old female child The presence of numerous undifferentiated cells is characteristic

22 ACUTE MYELOBLASTIC LEUKEMIA

Acute myeloblastic leukemia is a form of myelogenous leukemia hematologically characterized by the presence of a large number of myeloblasts in the peripheral blood (myeloblastemia) reflecting the abnormal proliferation of the same cells in the bone marrow These immature myeloid cell usually found to occupy a high percentage of the total leukocyte count are seen to be differentiating into more mature forms since they are accompanied by a few pro myelocytes myelocytes and metamyelocytes Fully mature segmented granulocytes may also be found in the circulating blood together with a limited number of nucleated red cells When the peripheral blood reveals only myeloblasts and polymorphonuclear neutrophils with few or no intermediate forms the phenomenon was called hiatus leukaemicus by Naegeli In the cytoplasm of not a few myeloblasts and leukoblasts the formation of azurophilic rods commonly known as Auer bodies has been demonstrated These bodies give positive peroxidase reactions and seem to be produced as a result of coalescence of azurophilic granule

While the myeloblasts found in acute leukemias are usually typical in morphologic characteristics in some cases the immature blast cells may show peculiarly complicated and folded nuclear configuration closely resembling those of monocytes These cells may be what Naegeli calls paramyeloblasts and when they predominate the blood picture the condition has been incorrectly designated as Naegeli type of acute monocytic leukemia or more correctly myelo monocytic leukemia In spite of Naegeli s dictum that monocytic leukemia is in reality a variant of the monocytic form it must be admitted that there exists a type of pure monocytic leukemia unaccompanied by granulocytic proliferation

The clinical manifestations of this disease are typical of acute leukemia in general with fairly well defined onset and rapidly progressing course Thrombo cytopenia often accompanied the pathologic changes in the bone marrow and leads to hemorrhagic symptoms While the terminal stage of chronic myelogenou leukemia may be characterized by signs of acute myeloblastic leukemia the two conditions can readily be differentiated on the basis of history Occasionally during the early stage of the disease the number of peripheral leukocytes may not be high or may even be subnormal which represents an aleukemic phase

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PLATE 41

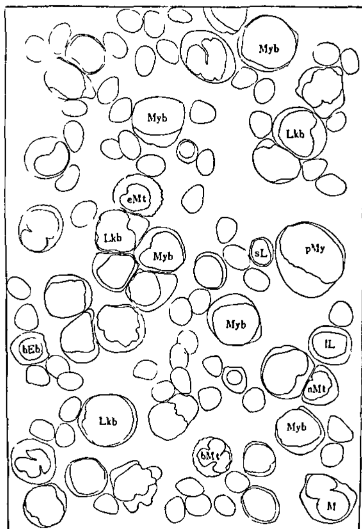
Acute Myeloblastic Leukemia
(1)

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PLATE 41

Acute Myeloblastic Leukemia

(1)



Myb Myeloblast
Lkb Leukoblast
nMt Neutrophilic metamyelocyte
eMt Eosinophilic metamyelocyte
sL Small lymphocyte
M Monocyte
bEb Basophilic erythroblast

Plate 41 is a case of acute myeloblastic leukemia

Plate 41 Acute Myeloblastic Leukemia (1)

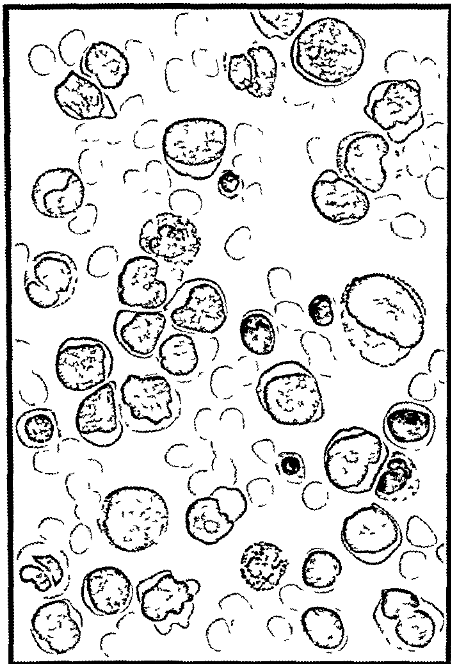


PLATE 42

Acute Myeloblastic Leukemia

(2)

PLATE 42

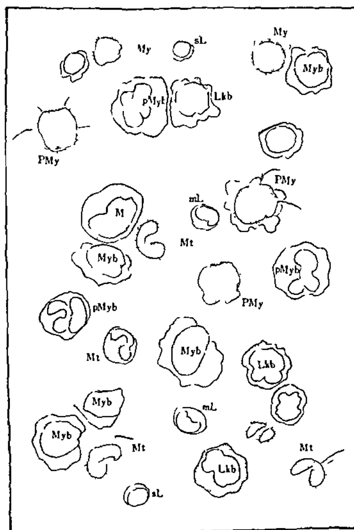
Acute Myeloblastic Leukemia

(2)

PLATE 42

Acute Myeloblastic Leukemia

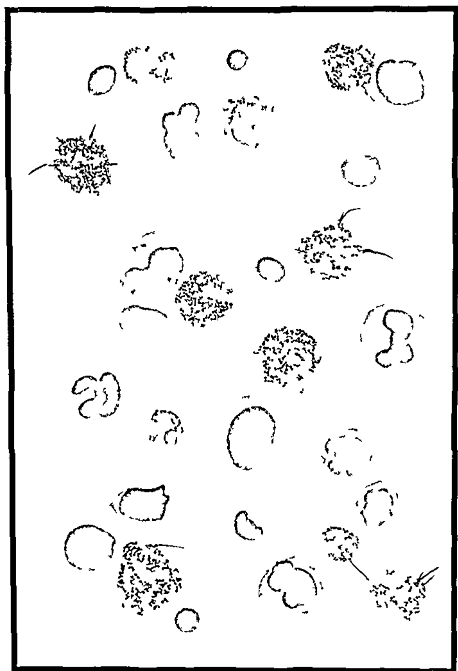
(2)



Myb Myeloblast
pMyb Paramyeloblast
Lku Leukoblast
PMy Promyelocyte
My Myelocyte
Mt Metamyelocyte
mL Mesolymphocyte
sL Small lymphocyte

Plate 42 shows the peroxidase positive cells (copper sulfate method) in the peripheral blood of a 7 year old patient with acute myeloblastic (paramyeloblastic) leukemia (Courtesy of the First National Tokyo Hospital)

Plate 42 Acute Myeloblastic Leukemia (2)



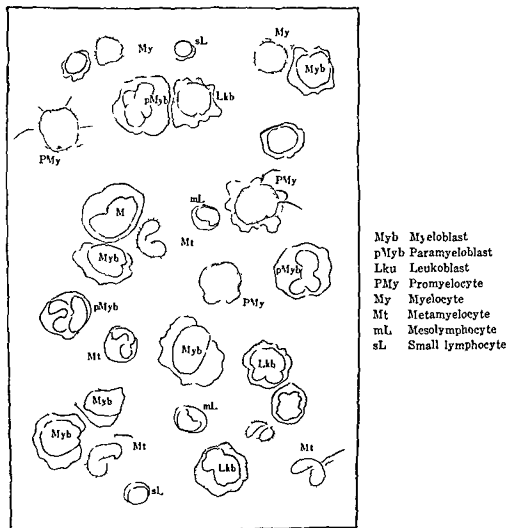
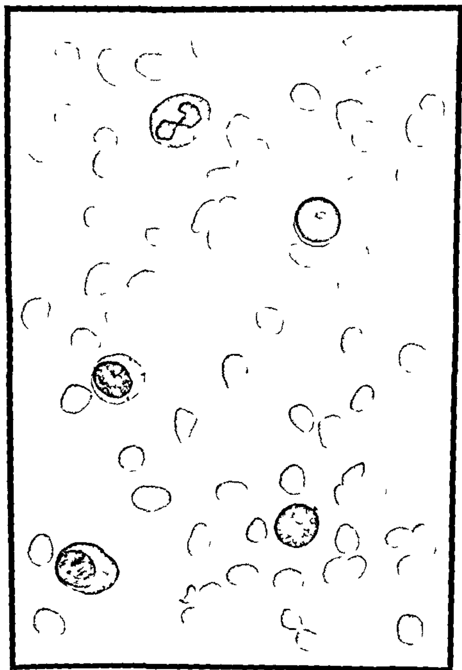


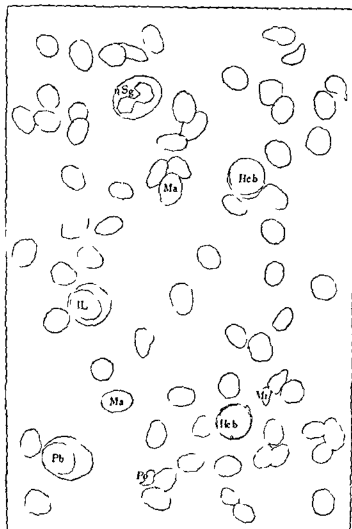
Plate 42 shows the peroxidase positive cells (copper sulfate method) in the peripheral blood of a 7 year old patient with acute myeloblastic (paramyeloblastic) leukemia (Courtesy of the First National Tokyo Hospital)

PLATE 43

Acute Aleukemic Leukemia

Plate 43 Acute Aleukemic Leukemia





Hcb	Hemocytoblast
lL	Large lymphocyte
Pb	Plasmablast
Mi	Microcyte
Ma	Macrocyte
Poi	Poikilocyte
nSg	Neutrophilic segmentocyte

Plate 43 is the peripheral blood picture of acute (aleukemic) leukemia in a 6 year old male child The presence of a few immature leukocytes (hemocytoblasts) constitutes positive evidence in favor of the diagnosis of leukemia

Plate 43 Acute Aleukemic Leukemia

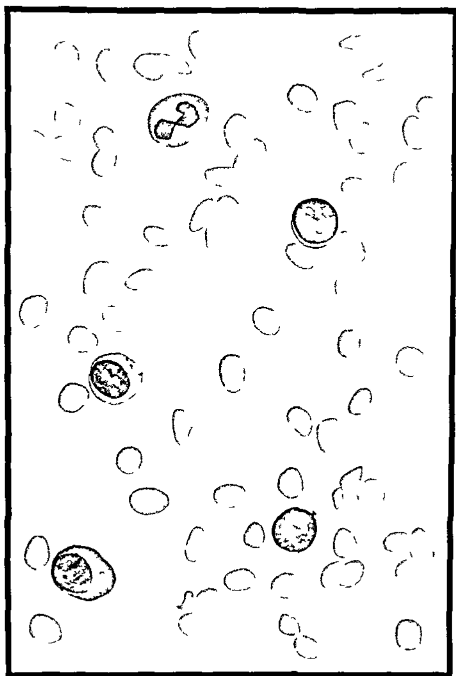
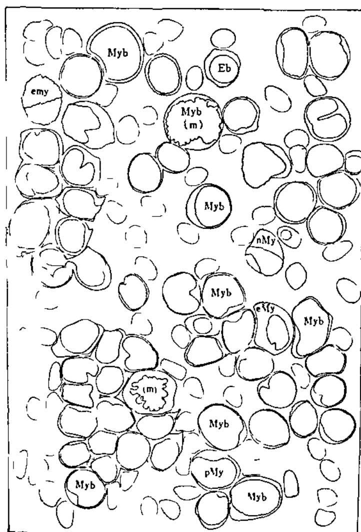


PLATE 44

Acute Myeloblastic Leukemia
(Myelogram)

PLATE 44

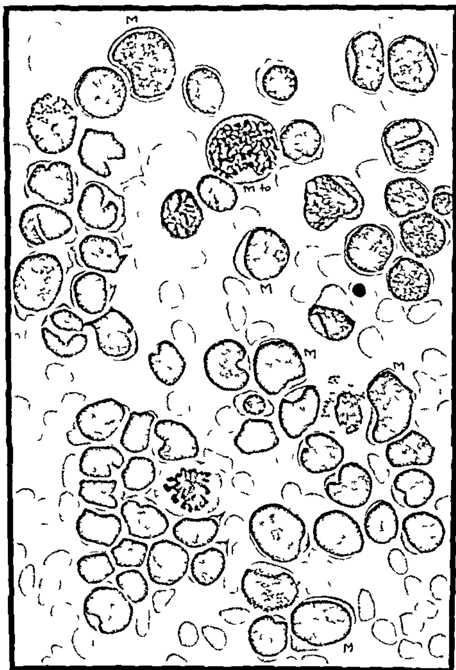
Acute Myeloblastic Leukemia
(Myelogram)



Myb Myeloblast
(m) Mitotic figure
pMy Promyelocyte
eMy Eosinophilic myelocyte
nMy Neutrophilic myelocyte
Eb Erythroblast

Plate 11 is the bone marrow picture in acute myeloblastic leukemia

Plate 44 Acute Myeloblastic Leukemia (Myelogram)



23 CHRONIC MYELOGENOUS LEUKEMIA

Chronic myelogenous leukemia is a slowly progressing proliferative disease of the blood and blood forming organs usually associated with heterotopic metaplasia in which the cells of the myeloid series are primarily involved Clinical manifestations of the disease are quite similar to those of the acute type the principal difference consisting of insidious onset mild symptoms and relatively long duration The prominent enlargement of the spleen with moderate hepatomegaly and lymphadenopathy is usually due to the process of extra medullary hematopoiesis occurring in these tissues Many of the early symptoms are referable to metabolic disturbances and the emergence of a bleeding tendency may be based on concomitant thrombocytopenia Loss in body weight anorexia polyhidrosis and increasing weakness are commonly seen while priapism and dysmenorrhea may occasionally be encountered

Almost without exception the hematologic characteristics of this disease consist of leukocytosis and often hyperleukocytosis in which the granulocytes in all stages of maturation participate In the majority of cases the granulocytes involved are of the neutrophilic type specifically designated as neutrophilocytic leukemia When the eosinophilic granulocytes are abnormally increased the term eosinophilocytic leukemia has sometimes been applied while the presence of an excessive number of basophilic granulocytes may justify the designation of baso philocytic leukemia The percentage of myeloblasts appearing in the peripheral blood is usually low the increasing proportion generally paralleling the advancing course of the disease There is also evidence of simultaneous stimulation of the erythroid series since the presence of normoblasts and sometimes erythroblasts can often be demonstrated Frequently the maturation of the nucleus and that of the cytoplasm may not take place in equal degrees (asynchromatism of Di Guglielmo) or the nucleus may show an undue degree of matured segmentation while the cytoplasm is still quite immature (dysmorphokaryocyte of Pittaluga) These abnormal findings may all be explained on the basis of disturbances in cellular metabolism so characteristic of this disease

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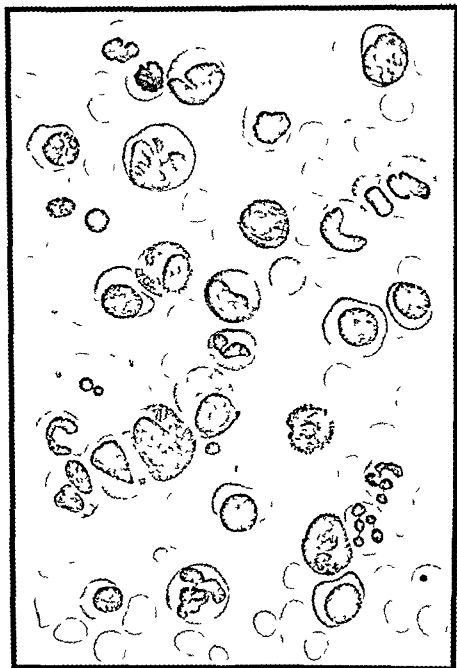
PLATE 45

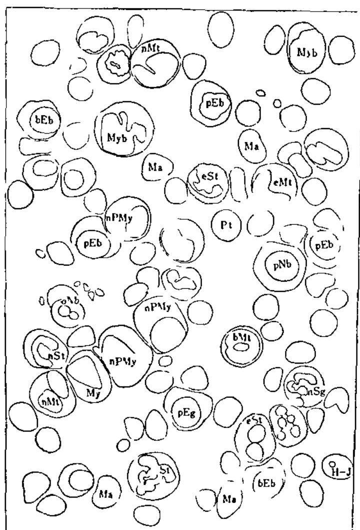
Chronic Myelogenous Leukemia
(1)

Myb Myeloblast
nPMy Neutrophilic promyelocyte
nMy Neutrophilic metamyelocyte
nSt Neutrophilic stab ceel
nSg Neutrophilic segmentocyte
eSt Eosinophilic stab cell
eSg Eosinophilic segmentocyte
bMt Basophilic metamyelobyte
bEb Basophilic erythroblast
pEb Polychromatophilic erythroblast
oNb Orthochromatic normoblast

Plate 15 is case of chronic myelogenous leukemia associated with a marked erythropietic reaction in the peripheral blood

Plate 45 Chronic Myelogenous Leukemia (1)





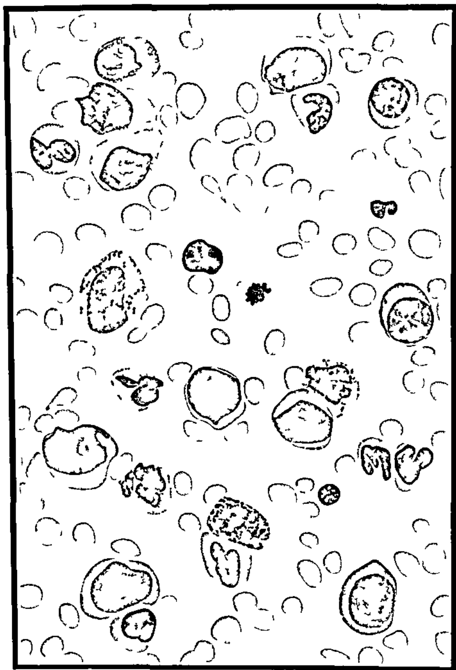
Myb *Myeloblast*
nPMy Neutrophilic promyelocyte
nMy *Neutrophilic* metamyelocyte
nSt Neutrophilic stab ceel
nSg *Neutrophilic* segmentocyte
eSt Eosinophilic stab cell
eSg *Eosinophilic* segmentocyte
bMt Basophilic metamyelobyte
bEb Basophilic erythroblast
pEb Polychromatophilic erythroblast
oNb Orthochromatic normoblast

Plate 15 is case of chronic myelogenous leukemia associated with a marked erythropietic reaction in the peripheral blood

PLATE [illegible]

Chronic Myelogenous Leukemia

2



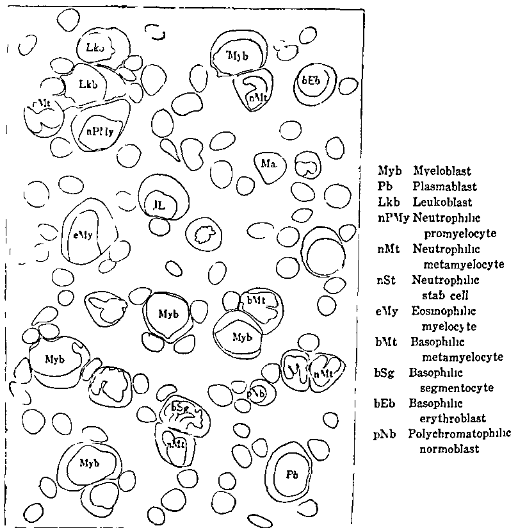


Plate 46 depicts a typical blood picture in chronic myelogenous leukemia

24 EOSINOPHILIA AND EOSINOPHILIC LEUKEMIA

The numerical alteration of eosinophilic leukocytes in the peripheral blood may assume the form of either eosinophilia or eosinopenia depending upon the increase above or decrease below the normal level Although the changes in the number of circulating eosinophils are subject to diurnal variation as well as to a wide variety of physiologic conditions there are a large number of pathologic stimuli which produce these abnormalities Eosinophilia has for many years been associated with allergic disorders skin diseases parasitic infestations collagenosis or any condition in which foreign proteins act as the stimulating factors A peculiar type of transitory lung infiltration accompanied by peripheral eosinophilia known as Loeffler s syndrome as well as tropical eosinophilia both of unknown etiology presents clinical pictures closely simulating epituberculosis and pulmonary tuberculosis Certain infections notably scarlet fever chorea and erythema multiforme may be associated with eosinophilia In malignant diseases particularly tumors of the ovary and of serous surfaces and bones Hodgkin s disease and periarteritis nodosa eosinophilia may be a characteristic finding Eosinophils have often been found to furnish a clue in determining dangerous amounts of radiation in detecting stress and in evaluating responses to surgical trauma such as splenectomy A condition generally called familial eosinophilia has been observed to occur in the majority of members of several families representing probably a hereditary anomaly in which the morphologic abnormalities of the eosinophilic cells involve both the nuclear pattern and cytoplasmic granulation

Recent advances in endocrinology and hormonal chemistry have furnished a considerable amount of information concerning the physiology and pathology of the eosinophilic leukocytes The fact that certain ductless glands particularly the thyroid gonads adrenal cortex and anterior pituitary exert either stimulating or inhibiting effects on hemopoiesis is now firmly established Of especial significance in this connection is the relation between the hypophysio adrenocortical system and the fluctuation of leukocytes in which changes in eosinophil level appear to provide an important indication

Eosinophilic leukemia is a specific disease of the blood with all the typical manifestations of myeloid leukemia but characterized by an abnormal proliferation of eosinophilic granulocytes in the bone marrow and accompanied by extensive infiltrations of various organs with these cells The disease is apparently rare since many observers have firmly refused to consider the diagnosis unequivocal unless the requirements of leukemic criteria are met with reasonable satisfaction However there are well studied cases of granulocytic leukemia in which the peripheral blood shows an overwhelming preponderance of eosinophilic leukocytes in all stages of maturation Clinically this form of leukemia may be either acute or chronic the average duration of illness being 1–2 years The chronic type was first reported by Stillman (1912) and the acute form by Seemann and Sajewa (1928)

PLATE 47

Eosinophilic Leukemia

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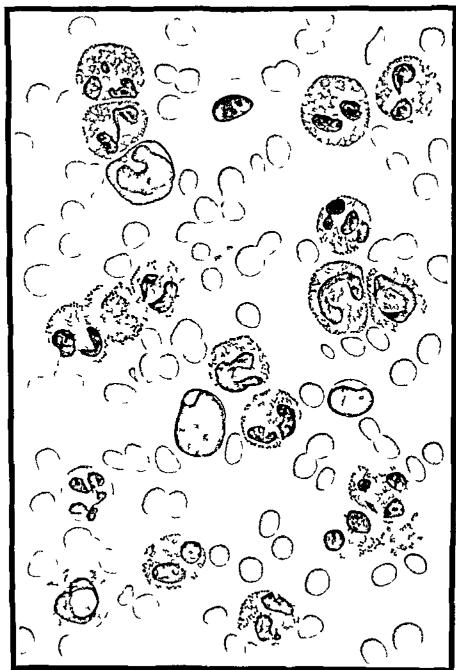
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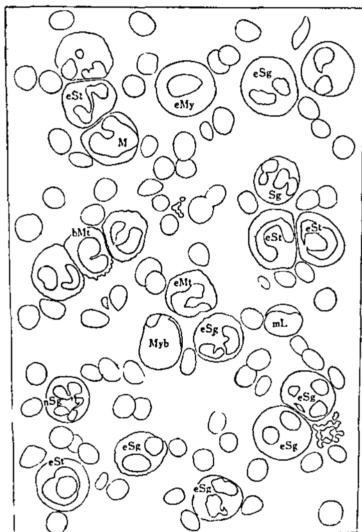
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Plate 47 Eosinophilic Leukemia

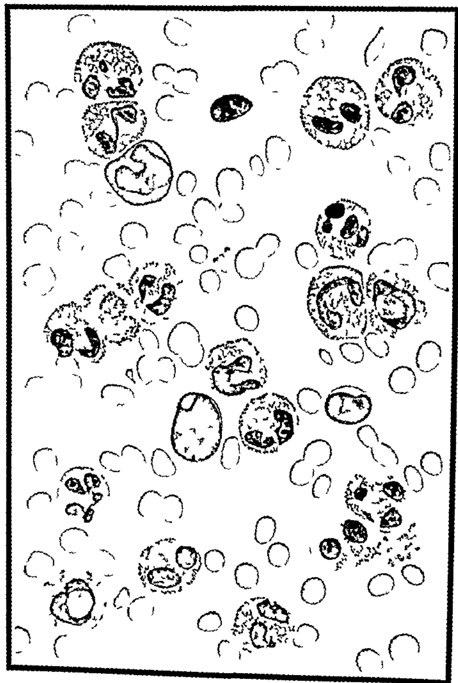




Myb	Myeloblast
nSg	Neutrophilic segmentocyte
eSg	Eosinophilic segmentocyte
eSt	Eosinophilic stab cell
eMy	Eosinophilic myelocyte
bMt	Basophilic metamyelocyte
mL	Mesolymphocyte
M	Monocyte

Plate 47 shows a case of probable eosinophilic leukemia in a 2 5 year old male child with hepatomegaly (3 fingers) in whom the leukocyte counts varied from 60 000 to 100 000 Occasionally the eosinophils were found to be as high as 80 per cent Both stool examination and muscle biopsy were entirely negative for parasites

Plate 47 Eosinophilic Leukemia



25 HODGKIN S DISEASE

Hodgkin s disease is generally regarded as a form of lymphoma or granuloma primarily involving the lymphatic tissue and histologically characterized by the polycellular composition of the affected lymph nodes The pathognomonic feature is the presence of Sternberg or Dorothy Reed cells which are giant cells 10 to 40 microns in diameter with abundant cytoplasm either acidophilic or basophilic and usually multilobed or multinucleated containing prominent nucleoli A peculiar group of cases presenting multiple swelling of lymph nodes was first described by Thomas Hodgkin in 1832 and Jackson and Parker (1944) distinguished three separate subgroups of this disease (1) Hodgkin s granuloma the most common type with protean manifestations (2) Hodgkin s paragranuloma a benign type in which the involved nodes contain mostly the adult lymphocytes and (3) Hodgkin s sarcoma a highly malignant true neoplasm seen in aged individuals

Starting with a painless gradual enlargement of one or more groups of superficial lymph nodes the process spreads to other tissues of the respiratory digestive cardiovascular genito urinary and nervous systems as well as the skin and bones The systemic manifestations include chill fever lassitude pain and loss of weight finally terminating in anemia cachexia and other severe constitutional symptoms

Hematologically aside from anemia often hemolytic in nature the leukocyte count may vary from definite reduction to marked increase There is a tendency to neutrophilia in cases with deep lymph node involvement while absolute lymphocytopenia is rather constant Monocytosis of up to 10 per cent may occur Eosinophilia is generally encountered at one stage or another during the course of illness and counts as high as 20-90 per cent of the total white cells may be found Ludman and Spear (1957) observed a case in which many abnormal primitive reticulum like cells were present in the peripheral blood These cells were larger with irregular and indistinct contours and some pseudopod formation While radiotherapy and administration of alkylating agents may produce good temporary results the extreme reduction in the number of thrombocytes may give rise to hemorrhagic symptoms particularly purpuric spots of the skin

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PLATE 48

Hodgkin's Disease

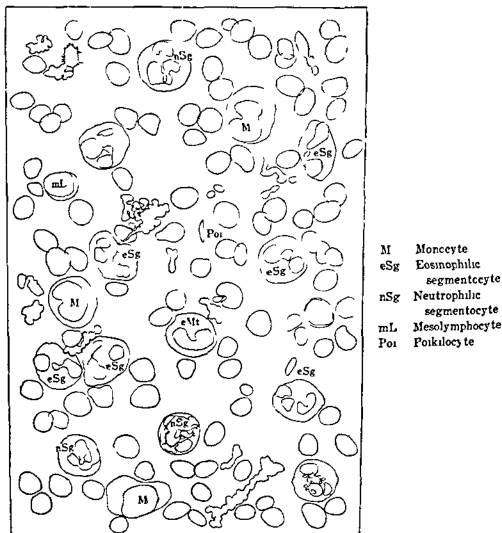
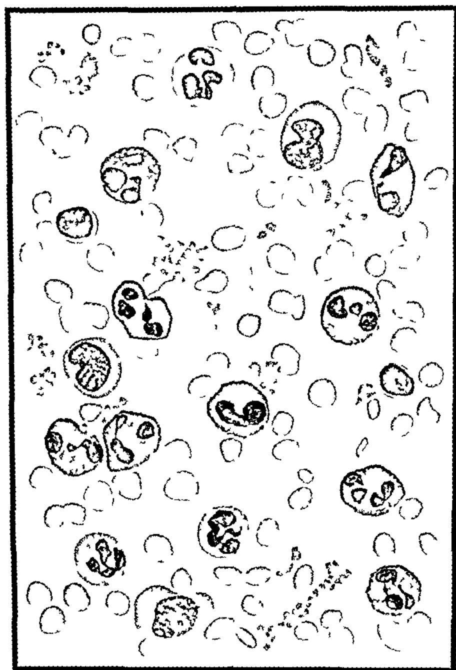


Plate 48 is a typical case of Hodgkin's disease with terminal eosinophilia observed and reported by W W Cardozo and K Kato

Plate 48 Hodgkin's Disease



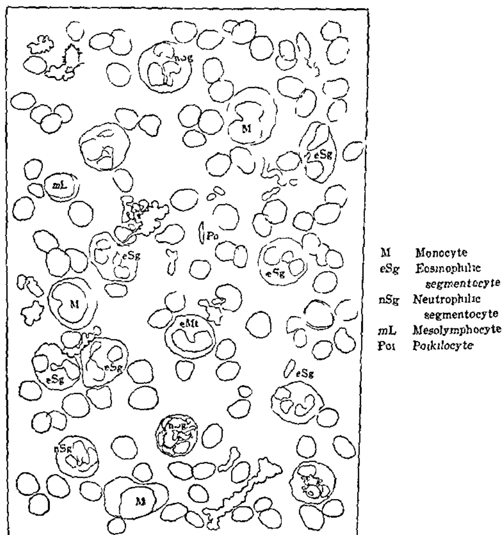


Plate 48 is a typical case of *Hodgkin's* disease with *terminal* eosinophilia observed and reported by W W Cardozo and K Kato

26 PERIARTERITIS NODOSA

Periarteritis nodosa (Kussmaul and Meier 1866) is a form of reactive panarteritis affecting all layers of the small and medium sized arteries throughout the body with production of inflammatory nodules along the outer wall No specific etiologic agent has yet been discovered but the nature of tissue changes strongly suggests an allergic origin possibly an anaphylactic type of hypersensitivity Rich (1942) has succeeded in the experimental production of characteristic lesions in rabbits by the repeated injection of horse serum Moreover the condition has been seen in *frequent association with asthma* serum sickness rheumatic diseases or sulfonamide reactions Engfeldt and Zetterstrom (1956) even designated this condition as disseminated eosinophilic collagen disease The focal lesions of periarteritis nodosa show degeneration necrosis and exudation preceded by intensitive infiltration by lymphocytes and granulocytes particularly eosinophils The development of multiple small arterial aneurysms may lead to either fibrosis or rupture with hemorrhage or ecchymosis while the changes in the intima may produce thrombosis and arterial obstruction The ultimate organization of the adventitial lesions gives rise to characteristic nodules which can be palpated along the course of the artery Such synonyms as essential polyangiitis necrotizing arteritis panarteritis or polyarteritis acuta nodosa have been applied to this disease

The clinical manifestations of periarteritis nodosa are extremely variable depending largely on the arteries most involved which may be gastrointestinal hepatosplenic cardiorenal or organic nervous in location Cutaneous and internal hemorrhages are not infrequent

Hematologically the peripheral blood reveals the presence of secondary anemia and from moderate to severe leukocytosis which is essentially a leukemoid reaction The most striking hematologic aspect is the frequent occurrence of eosinophilia which may be as high as 84 per cent of the total white cell count (Mowrey and Lundberg) Since eosinophilia occurs in a variety of diseases careful differentiation is required in the diagnosis of periarteritis nodosa

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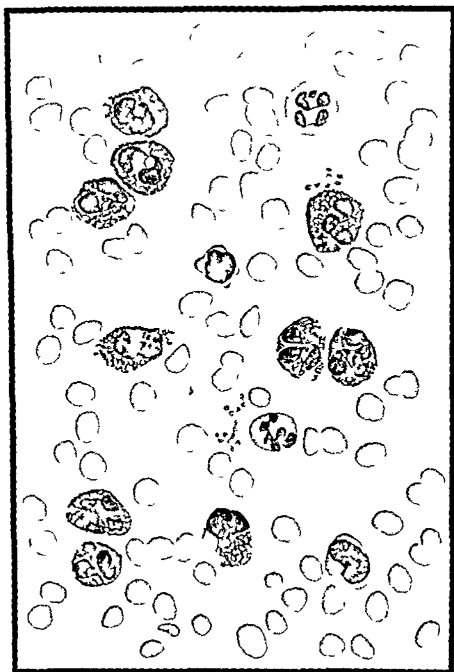
PLATE 49

Periarteritis Nodosa

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Plate 49 Periarteritis Nodosa



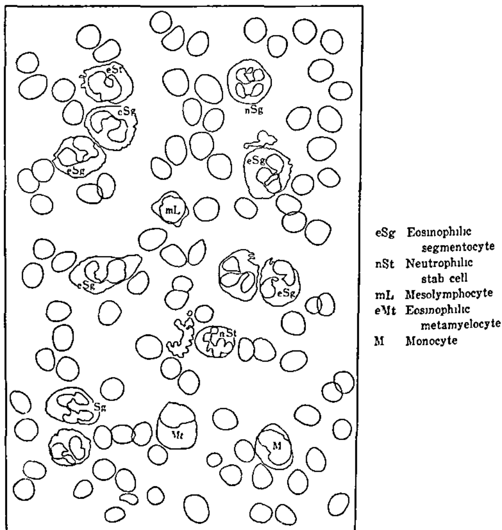


Plate 49 is a picture of eosinophilia in the peripheral blood of a patient with periarteritis nodosa

27 BASOPHILOCYTIC LEUKEMIA

Basophilocytic or basophilic leukemia is a rare variant of myeloid leukemia hematologically distinguished by the presence of peripheral leukocytosis consisting of a predominance of basophilic granulocytes representing all stages of maturation The incidence of this specific form of granulocytic leukemia is apparently low and its diagnosis seems to be even more controversial than for eosinophilocytic leukemia The blood is characterized by a marked leukocytosis due to the presence of numerous basophilic cells In one case observed by Joachim (1906) the peripheral blood contained 63 2 per cent of these cells and at autopsy the spleen liver and lymph nodes were greatly enlarged due chiefly to leukemic infiltration of basophilic cells as well as of other varieties of granulocytes Bone marrow preparations revealed the proliferative process involving the basophilic granulocytes

Other conditions showing a well defined increase of basophilocytes particularly in the response phase of chronic neutrophilocytic leukemia during treatment in the para leukemic state of myelofibrosis with metaplasia and in polycythemia vera according to Dameshek and Gunz must be carefully differentiated from true basophilic leukemia

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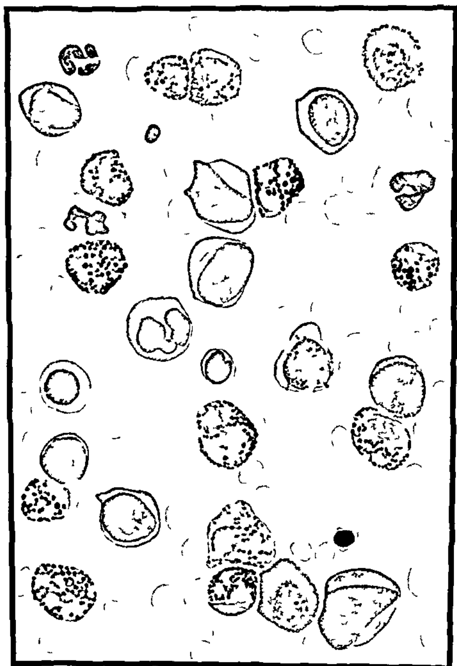
PLATE 50

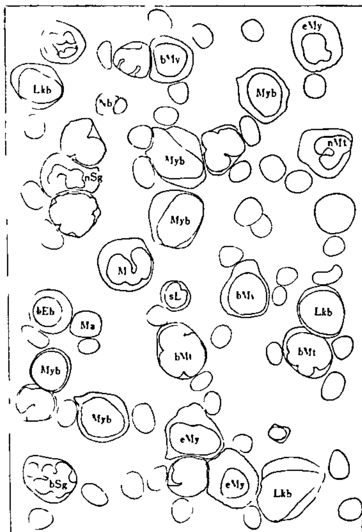
Acute Basophilic Leukemia

cas de myeloleucemie chronique, Gaz hebd d Soc méd de Bordeaux, 46 678 1925

Tomaszewski Z Ueber einen Fall von Mastzellenleukämie Fol haemat 12 115 1911

Plate 50 Acute Basophilic Leukemia





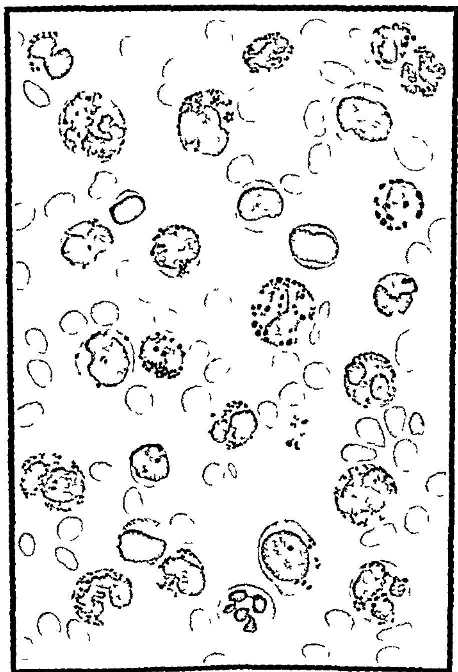
Myb	Myeloblast
M	Monocyte
Lkb	Leukoblast
bMy	Basophilic myelocyte
bMt	Basophilic metamyelocyte
bSg	Basophilic segmentocyte
nSg	Neutrophilic segmentocyte
eMy	Eosinophilic myelocyte
sL	Small lymphocyte
Ma	Macrocyte
Nb	Normoblast

Plate 50 is a case of acute basophilic leukemia (Courtesy of Drs W A Groat T Wyatt S Zimmer and R Field)

PLATE 51

Subacute Basophilic Leukemia

Plate 51 Subacute Basophilic Leukemia



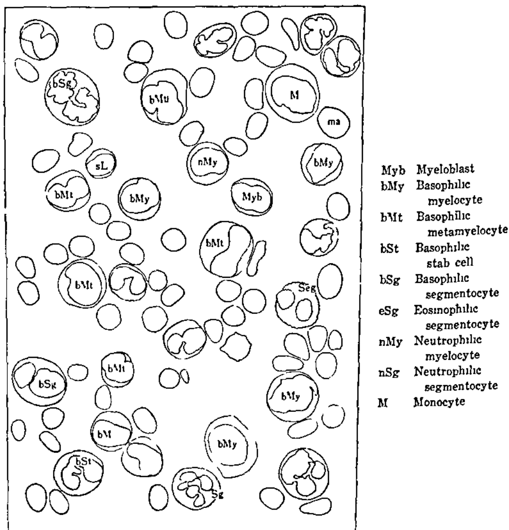


Plate 51 shows a case of subacute basophilic leukemia in a middle aged male

28 MASTOCYTOSIS AND MAST CELL LEUKEMIA

The question of whether the basophilic leukocyte and the tissue mast cell are hematologically and cytologically identical has not as yet been completely settled Ehrlich (1877 1879) first stated that these two cells had little in common the one produced in the bone marrow the other in the tissue This was despite the fact that the basophilic granules so abundantly present in both give metachromatic staining reactions moreover these granules appear to be the sources of both heparin and histamine the substances maintaining a certain *relationship to each other under varying conditions However upon close mor*phologic examination of these cell types the differences in regard to the shape and size of the nucleus the distribution pattern as well as the exact staining quality of the granules and the physiologic location under normal conditions appear to be impressive enough to raise a doubt about the absolute identity of these two cells

The occurrence of mastocytosis and mastocytoma has been observed by several investigators in connection with urticaria pigmentosa in which the skin nodules are characterized by large collections of mast cells Hissard and his co-workers (1951) described a case of mastocytosis and found numerous tissue mast cells in the lymph nodes bone marrow and many other tissues The term hematodermia was applied by these authors to the skin lesions with mast cell infiltrations while Sagher (1956) advocated the collective term mast cell disorders to include all instances of mast cell hyperplasia All these observations naturally lead to an assumption as to the existence of mast cell leukemia as a distinct entity The first case of urticaria pigmentaosa reported by Ellis (1949) indicated a tendency for this disease to be generalized and in one of the more recently described cases reported by Waters and Lacson (1957) approximately 25 per cent of the nucleated cells were found on sternal marrow aspiration to be tissue mast cells In addition a moderate number of these cells was also seen at the periphery of blood smears It is likely therefore that urticaria pigmentosa *is from the first a systemic disease with a mast cell proliferation beginning in the* skin and later disseminating to other tissues When the proliferating cells begin to appear in the blood the condition becomes mast cell leukemia

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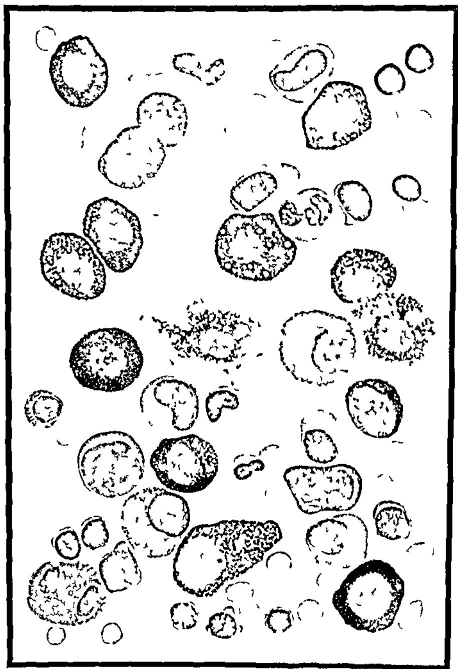
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PLATE 52

Mast Cell Lenkemia
(Myelogram)

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Sagher F Cohen C and Schorr S Concomitant bone changes in urticaria pigmentosa J Invest Dermat 18 425 1952
Reilly E Shintani J and Goodman J Systemic mast cell disease Arch Dermat & Syph 71 561 1955
Waters W J and Lacson P S Mast cell lekemia presenting as urticaria pigmentosa Report of a case Pediat 19 1033 1957

Plate 52 Mast Cell Leukemia (Myelogram)



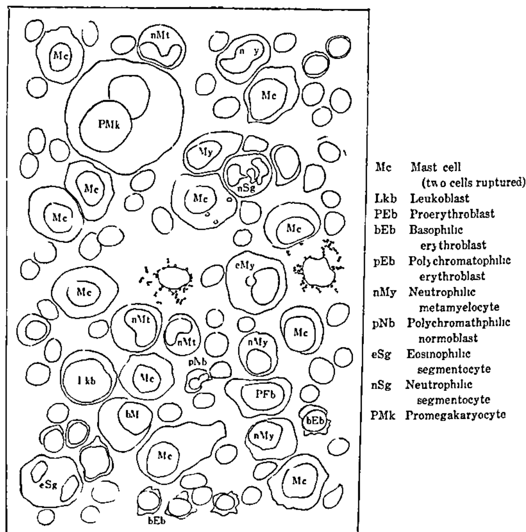


Plate 52 is the bone marrow picture showing a marked mastocytosis in a 5 year old male child The peripheral leukocyte counts varied from 7 200 to 20 300 and a few mast cells were seen on the smear preparations (Courtesy of Drs W J Waters and P S Lacson)

29 ACUTE LYMPHOBLASTIC LEUKEMIA

Acute lymphoblastic leukemia with all the typical manifestations of acute leukemia generally is a rapidly progressing disease of the blood characterized by a monotonous proliferation of lymphoblasts in the hemopoietic tissues with resultant lymphoblastemia in the peripheral blood Being considered as the determinant in the diagnosis of this disease the lymphoblasts exhibit little tendency to proceed towards the stages of further maturation although they are always accompanied by a few typical lymphocytes as well as by their progenitors the hemocytoblasts The disease is also called simply acute lymphatic leukemia without emphasizing the predominance of lymphoblasts Occasionally the disease is clinically designated as subacute lymphatic leukemia when its progress is somewhat slower than that of the typical acute form

The symptoms of acute lymphoblastic leukemia are essentially those seen in any acute type but lymphadenopathy and splenomegaly are more pronounced than in other forms Purpuric spots and bleeding manifestations may be frequent but ulcerative or necrotic changes of the oral mucous membrane are rare

The peripheral leukocyte count may vary greatly from time to time a phenomenon common to all types of acute leukemia Gosio (1930) once suggested that the variations occurring in a short period of time may be related to the abnormal activity of leukolytic enzymes in the blood During the initial stage of the disease the absence of leukocytosis may offer difficulties in differential diagnosis The pathognomonic cell the lymphoblast is the most immature cell of the lymphatic series possessing basophilic cytoplasm devoid of any granules and a round or oval nucleus composed of fine chromatin somewhat coarser than that of the hemocytoblast One or two relatively large nucleoli are distinctly visible The prolymphocyte may be identified by the tendency of the nucleus to develop a shallow indentation on one side with nuclear chromatin still further condensed than that of its predecessor Lymphoblasts with an irregularly shaped nucleus which Naegeli called paralymphoblasts as well as cells with a vacuolated cytoplasm (Gamberini) may also be seen

Rieder cell leukemia is a designation formerly employed simply to describe the morphologic peculiarities of the atypical leukemic cells probably lymphoblastic in essential nature The cells here concerned which are practically never seen in normal blood are relatively large in size with an average diameter of about 10 microns The most unusual feature of this cell is the coiled curved or convoluted but never distinctly segmented configuration of the nucleus and its chromatin structure is quite similar to that normally typical of lymphoblasts or of myeloblasts with clearly demonstrable nucleoli The cytoplasm stains deep blue giving an impression of being immature but the existence of any granules specific or nonspecific is not apparent Pieder cells are seen almost exclusively in leukemia usually lymphatic in type either acute or chronic in course although they have occasionally been encountered in other conditions in which the hemopoietic tissue is extensively or intensively involved by neoplasms or infection

Incidentally while the Rieder cell is considered to be an atypical form of lymphoblast arising under pathologic conditions it is impossible to decide whether it is only another name applied to what Naegeli termed paralymphoblast

or paramyeloblast It has been stated that even the myeloblast particularly in acute leukemia may show several wide and deep indentations suggesting lobulation of the nucleus which may represent a more rapid maturation as compared with the cytoplasm or the phenomenon of asynchronism of Di Guglielmo

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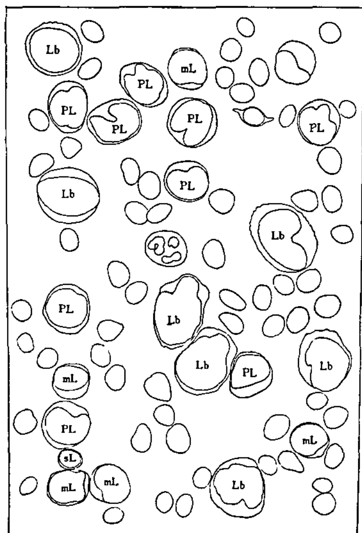
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PLATE 53

Acute Lymphoblastic Leukemia



Lb	Lymphoblast
PL	Prolymphocyte
mL	Mesolymphocyte
sL	Small lymphocyte

Plate 53 is a case of acute lymphoblastic leukemia

Plate 53 Acute Lymphoblastic Leukemia

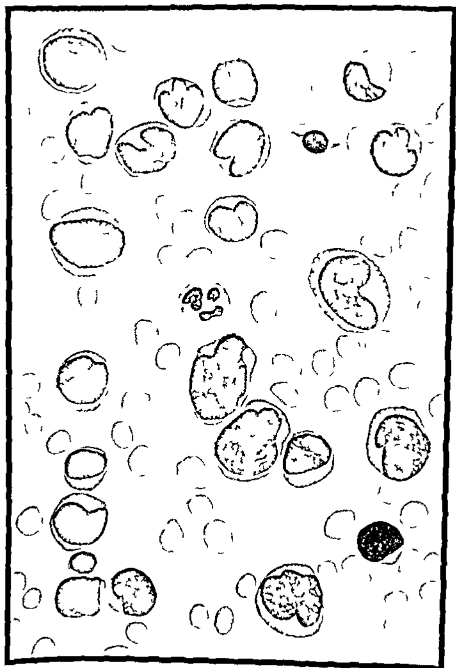
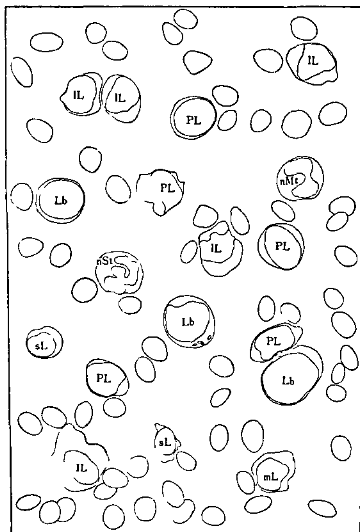


PLATE 54

Subacute Lymphatic Leukemia

(1)



Lb	Lymphoblast
lL	Large lymphocyte
mL	Mesolymphocyte
sL	Small lymphocyte
PL	Prolymphocyte
nMt	Neutrophilic metamyelocyte

Plate 54 is a case of subacute lymphocytic leukemia in which the immature stages of lymphocytes are represented by a few lymphoblasts and prolymphocytes

Plate 54 Subacute Lymphatic Leukemia (1)

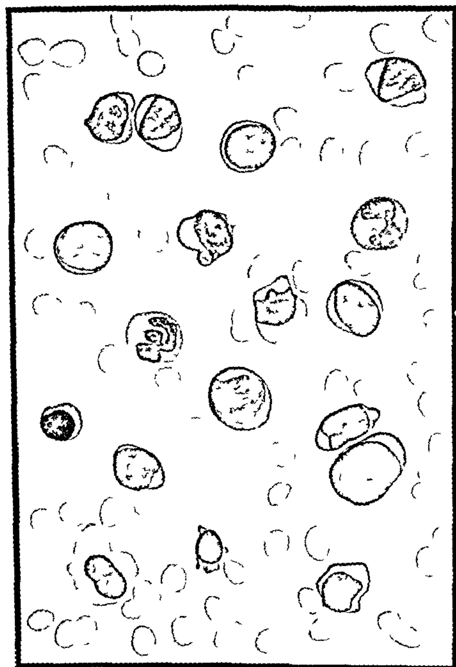
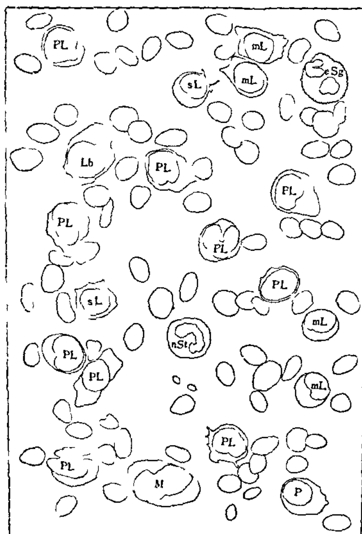


PLATE 55

Subacute Lymphatic Leukemia

(2)



Lb	Lymphoblast
PL	Prolymphocyte
lL	Large lymphocyte
mL	Mesolymphocyte
sL	Small lymphocyte
M	Monocyte
eSg	Eosinophilic segmentocyte
nSt	Neutrophilic stab cell

Plate 55 shows subacute lymphocytic leukemia in which the differentiation of lymphoblasts from prolymphocytes is difficult morphologically

Plate 55 Subacute Lymphatic Leukemia (2)

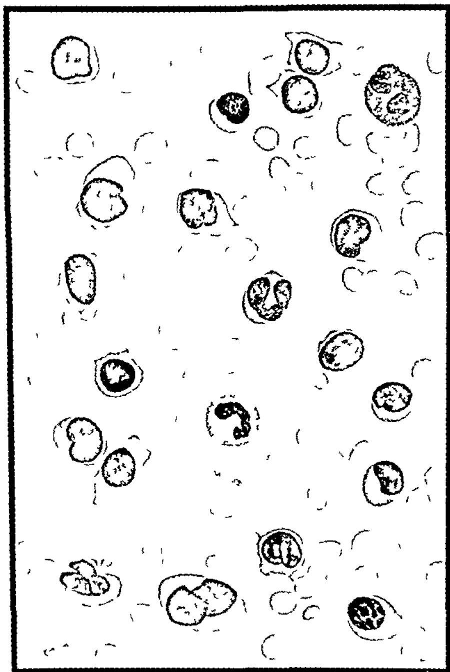
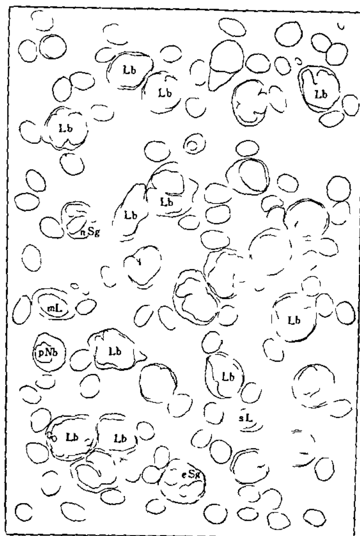


PLATE 56

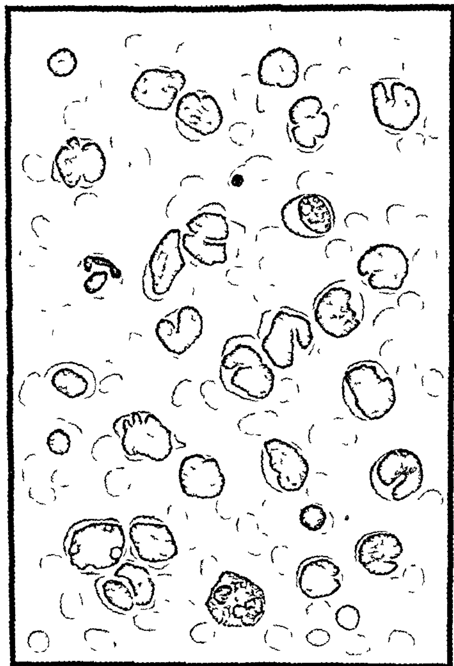
Rieder Cell Leukemia



Lb Lymphoblast
mL Mesolymphocyte
sL Small lymphocyte
eSg Eosinophilic segmentocyte
nSg Neutrophilic segmentocyte
pNb Polychromatophilic normoblast

Plate 56 is the peripheral blood picture in Rieder cell leukemia (Courtesy of Dr E V Kandel)

Plate 56 Rieder Cell Leukemia



30 CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia also called chronic lymphoid or lymphogenous leukemia is a proliferative disease primarily of the lymphoid tissues as manifested by a moderate lymphocytosis in the peripheral blood and clinically *characterized by the development of highly variable and exceedingly protean* symptoms

In discussing the symptomatology of this disease Dameshek and Gunz (1958) distinguish between the typical or aggressive form usually seen in young adults and the benign or asymptomatic type occurring more frequently in older patients *In the typical form the earliest manifestation is that of lymphadeno* pathy involving first the superficial nodes but later extending to those situated in deeper locations The tumefaction sometimes developing in the salivary or lacrimal glands may produce what is known as Mikulicz syndrome and the enlargement of the mesenteric lymph nodes together with the presence of splenic tumor may make the abdomen feel like a sack of potatoes The skin at first pale and sallow in appearance may begin to show leukemic changes (leukemia cutis) or nonspecific lesions (leukemids) Anemia which may be autoimmune hemolytic in nature weakness hematuria priapism and even neurologic symptoms are noted The serum proteins exhibit changes starting with initial hyper *globulinemia with associated hypoalbuminemia but ending with terminal hypo* gammaglobulinemia In the benign or asymptomatic form the disease may hardly be considered leukemic since there are no typically leukemic manifestations which interfere with the daily routine of life

Hematologically the disease is typified by a definite lymphocytosis both relative and absolute regardless of the total number of leukocytes in the peripheral blood Hirschfeld (1925) observed a case with only 1800 leukocytes of which 95 per cent were small lymphocytes There are always a few lympho blasts in the peripheral blood but the great majority are either prolymphocytes or mature lymphocytes The myeloid cells together with monocytes and normo blasts may be present in limited numbers The bone marrow reveals a picture of monotonous hyperplasia in which practically all the stages in the maturation of lymphoid cells can be demonstrated

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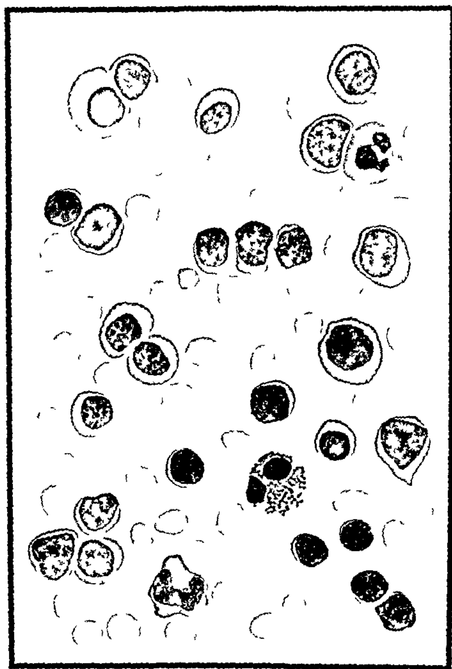
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PLATE 57

Chronic Lymphatic Leukemia

1925
Richter M N Observations on the hemohistioblast of Ferrata Am J Med Sc 169 336 1925
Rowe S N Mikulicz s syndrome with chronic lymphatic leukemia New England J M 202 863 1930

Plate 57 Chronic Lymphatic Leukemia



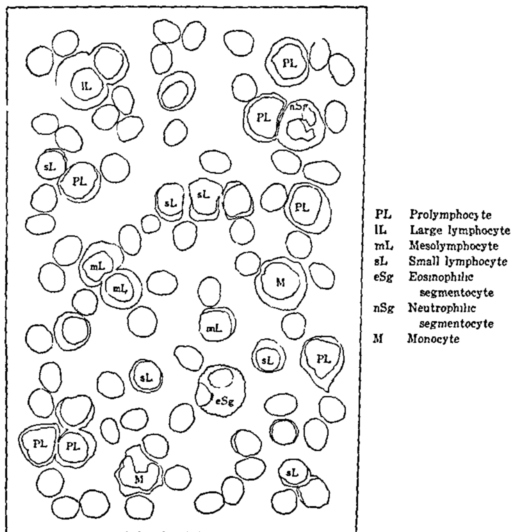
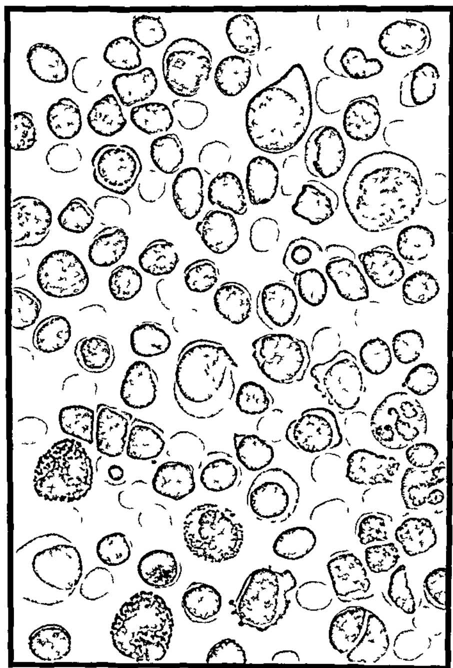


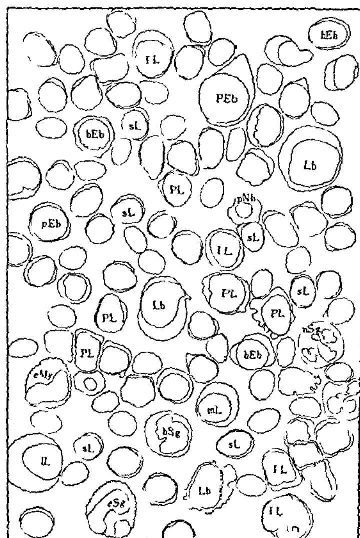
Plate 57 is the peripheral blood picture in chronic lymphocytic leukemia (Courtesy of Drs S Hibino and K Asai)

PLATE 58

Chronic Lymphatic Leukemia
(Myelogram)

Plate 58 Chronic Lymphatic Leukemia (Myelogram)

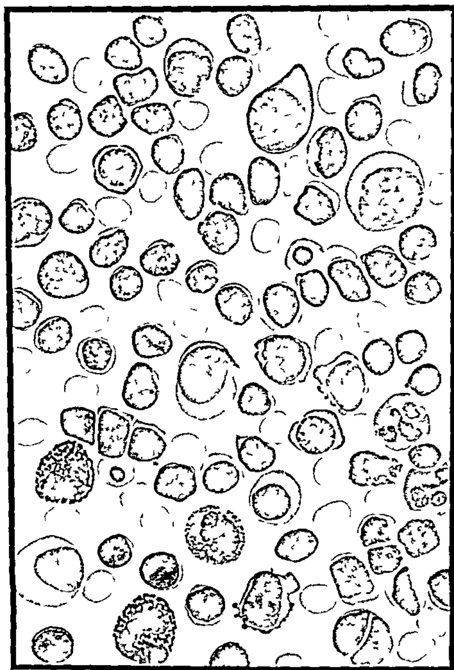


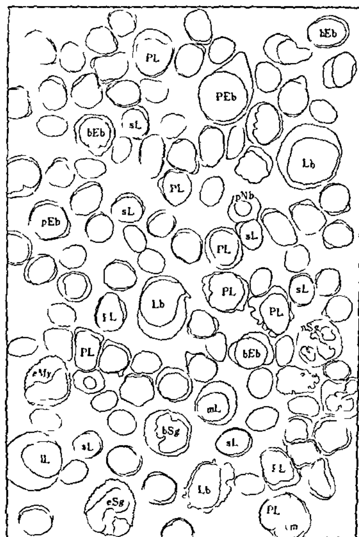


Lb	Lymphoblast
PL	Prolymphocyte
lL	Large lymphocyte
mL	*Mesolymphocyte*
sL	Small lymphocyte
nSg	Neutrophilic segmentocyte
eMy	Eosinophilic *myelocyte*
eSg	Eosinophilic segmentocyte
bSg	Basophilic segmentocyte
bEb	Basophilic *erythroblast*
pEb	Polychromatophilic erythroblast
PEb	*Proerythroblast*
(m)	Mitotic figure

Plate 58 is the bone marrow picture in chronic lymphocytic leukemia (Courtesy of Drs S Hibino and K Asai)

Plate 58 Chronic Lymphatic Leukemia (Myelogram)





Lb	Lymphoblast
PL	Prolymphocyte
lL	Large lymphocyte
mL	Mesolymphocyte
sL	Small lymphocyte
nSg	Neutrophilic segmentocyte
eMy	Eosinophilic *myelocyte*
eSg	Eosinophilic segmentocyte
bSg	Basophilic segmentocyte
bEb	Basophilic erythroblast
pEb	Polychromatophilic erythroblast
PEb	*Proerythroblast*
(m)	Mitotic figure

Plate 58 is the bone marrow picture in chronic lymphocytic leukemia (Courtesy of Drs S Hibino and K Asai)

PLATE 59

Lymphosarcoma Cell Leukemia

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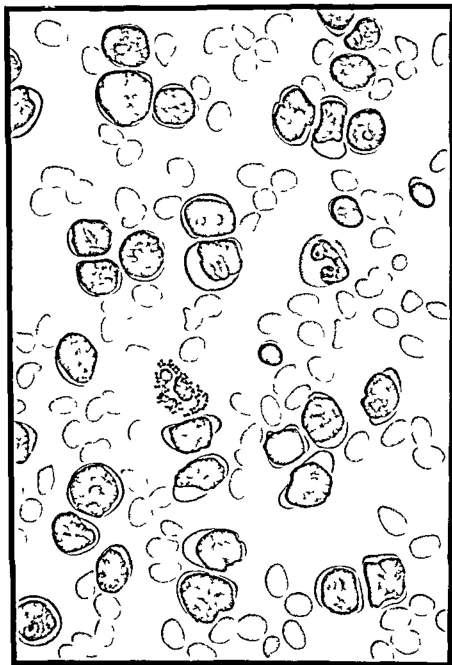
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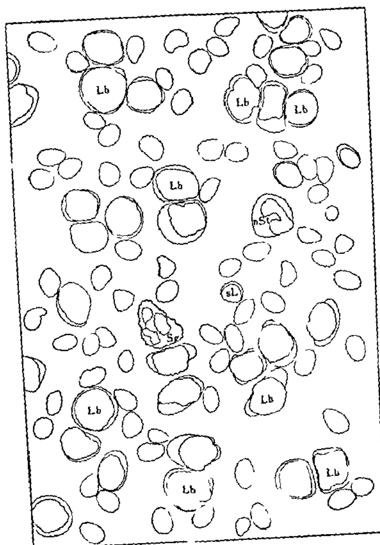
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Plate 59 Lymphosarcoma Cell Leukemia

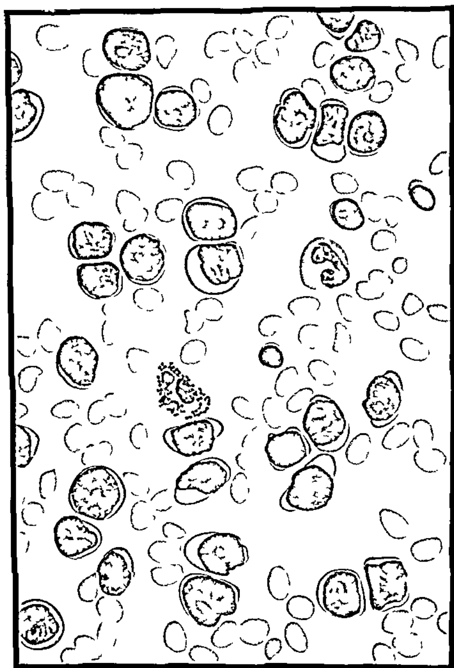




Lb Lymphoblast
nSt Neutrophilic stab cell
sL Small lymphocyte
eSg Eosinophilic segmentocyte
(many lymphosarcoma cells are present)

Plate 59 is a case of lymphosarcoma cell leukemia developing after irradiation therapy observed by A Brunschwig and K Kato

Plate 59 Lymphosarcoma Cell Leukemia



32 CONGENITAL LEUKEMIA

Congenital leukemia is a rare blood disorder of the newborn occurring with all the leukemic features as a result of abnormal proliferation of leukocytes and having an onset during the intrauterine life Since leukemic mothers do not necessarily give birth to leukemic babies the disease does not represent a hereditary or familial condition (Erf 1947) However it is plausible that some intrinsic factors may exert an influence on the etiology of this disorder for there are a few instances in which leukemia occurs in combination with other congenital malformations It is also feasible to a sume that an exogenous agent (leukemogen) may be involved for the same reason particularly ionizing radiations frequently applied on the maternal pelvis in diagnostic x ray examination Dameshek and Gunz (1958) reviewed the literature but found no information on maternal irradiation and emphasize the necessity of carefully evaluating the possible benefits of radiation applied during pregnancy in relation to the development of congenital leukemia This disease was first described by Sanger in 1888 and Siefart (1898) observed the relation of placental edema to fetal leukemia Erythroblastosis fetalis congenital syphilis and septicemia must be differentiated from congenital leukemia by appropriate diagno tic tests

The most significant symptoms are spontaneous hemorrhages from the skin and mucous membranes nodular skin infiltrations lymphadenopathy fever and pallor The presence of concomitant defects elsewhere in the body may be an aid in correct diagnosis

The blood reveals a definite leukocytosis usually due to an increase in the percentage of granulocytes but a few instances had been shown to be lymphatic in nature The associated anemia may be remarkable but is often hyperchromic Thrombocytopenia may be present and may explain the bleeding symptoms The bone marrow usually confirms the myeloid hyperplasia and in the patient observed by Morrison Samwick and Rubinstein (1939) the proliferation of chloroma cells was demonstrated even in the circulating blood

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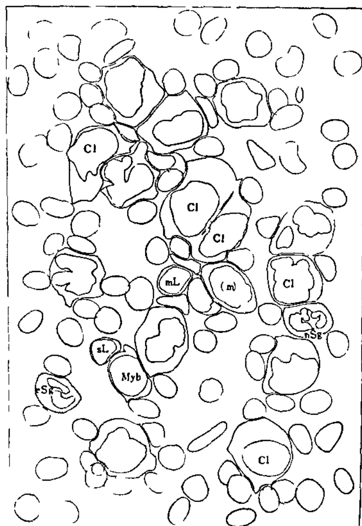
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PLATE 60

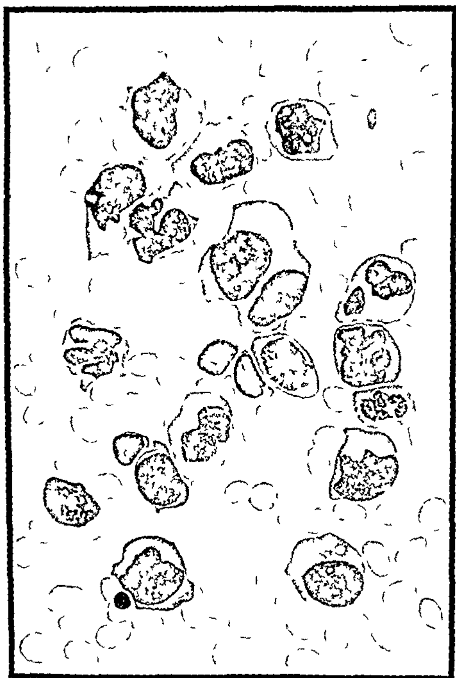
Congenital Leukemia



Cl	Chloroma cell
(m)	Mitotic figure
Myb	Myeloblast
mL	Mesolymphocyte
sL	Small lymphocyte
nSg	Neutrophilic segmentocyte
eSg	Eosinophilic segmentocyte

Plate 60 is a case of congenital leukemia associated with chloroma (Courtesy of Drs M Morrison A A Samwick and P I Rubinstein)

Plate 60 Congenital Leukemia



33 CHLOROMA AND CHLOROLEUKEMIA

Chloroma or more accurately chloroleukemia is a tumerous manifestation of leukemia usually occurring in children and young adults characterized by the development of invasive tumor like growths of greenish color composed of primitive cells in various organs and tissues and by the presence of numerous chloroma cells in the blood The most striking changes involve the periosteum and ligamentous structures at various locations in addition to the leukemic transformation of the bone marrow

The name meaning green tumors was first used by King in 1853 although the earliest description of the disease is credited to Allen Burns (1823) Despite intensive studies the greatest source of confusion has centered around the proper classification of the pathognomonic cell so constantly seen in the peripheral blood The use of such terms as chloromyelosarcoma chlorolympho sarcoma chloroerythroblastoma and the like was advocated by various writers for the purpose of emphasizing the particular cell types involved Since the blood picture in the majority of cases is typified by a mixture of all varieties of blood cells in all conceivable proportions Klein and Steinhaus (1904) proposed to call the disease mixed cell chloroma After the close relationship between chloroma and leukemia had been conclusively established by Dock and Warthin (1904) Butterfield (1909) endeavored to unify the nomenclature by proposing the name chloroma cell More recent studies indicate the chloroma cell to be a variant of the monocyte (Amano) or even a monoblast derived directly from the histiocyte leading to a new designation monoblastotic chlorotic mono sarcomatosis

The early manifestations of chloroma consist of the development of orbital tumors with marked exophthalmos lymphadenopathy and rapidly progressing anemia Localized symptoms are referrable to any group of organs affected and like any case of acute leukemie pallor weakness bone pain necrotizing angina and bleeding tendencies are common Pressure symptoms include visual disturbances deafness and cranial palsies arising from tumor growths encroach ing upon the nervous tissue Pleural effusions and splenomegaly may be present X ray examination of the affected bones may reveal new bone formation of irregular configuration along the periosteum

Hematologically aside from the presence of severe anemia the multiplication of chloroma cells in the peripheral blood as well as in the bone marrow is most characteristic While leukocytosis is the rule the blood may be leukopenic or even aleukemic The pathognomonic cell is a large mononuclear element with a round or indented nucleus and the chromatin arrangement suggests the cell to be extremely primitive The cytoplasm is usually abundant and takes on a pale blue color on staining often presenting an irregular, wavy contour

The green pigment of the tumor is grossly observable on fresh specimens but fades on exposure to light and air It can however be temporarily restored by treatment with hydrogen peroxide and can be preserved by placing the tissue in glycerin The chemical nature of the pigment has not been satisfactorily identified but its relationship to bilirubin lipochrome choleglobin and porphyrin particularly protoporphyrin all arising from disturbed cytochrome synthesis has been seriously considered and experimentally demonstrated (Schultz et al)

PLATE 61

Chloroleukemia

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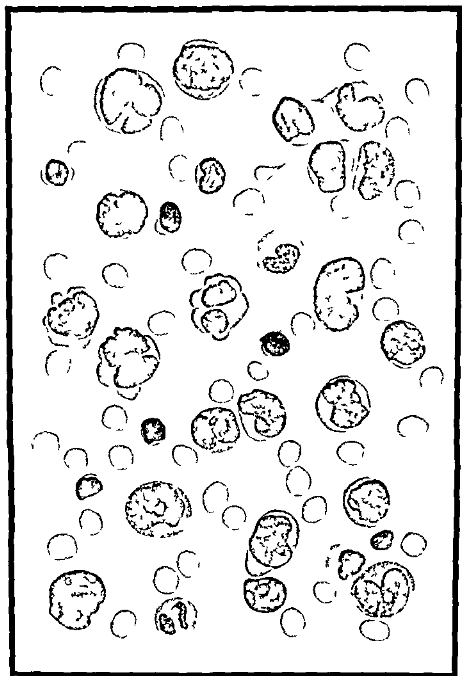
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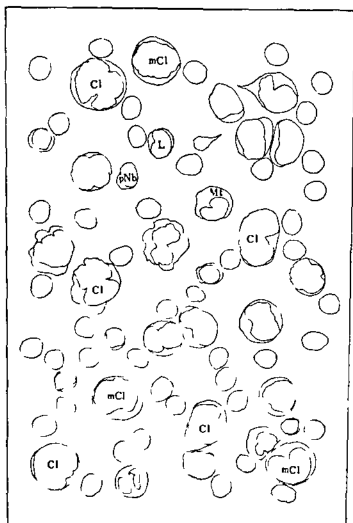
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Plate 61 Chloroleukemia

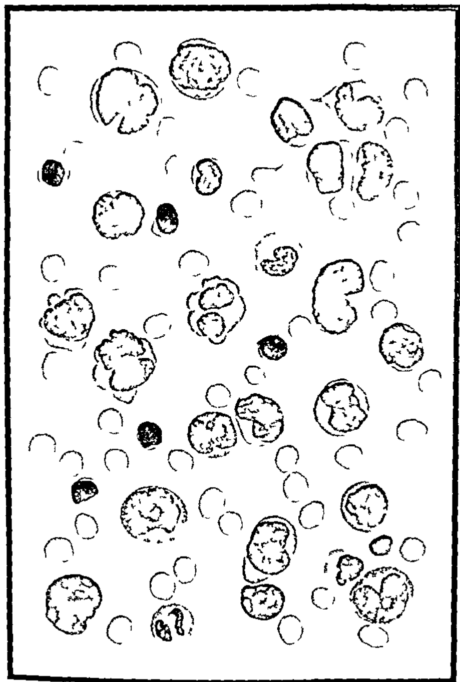


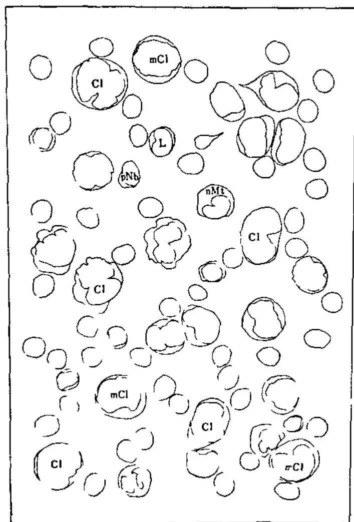


Cl Chloroma cell
mCl Myeloblastic chloroma cell
nMt Neutrophilic metamyelocyte
pNb Polychromatophilic normoblast
L Lymphocyte

Plate 61 shows the peripheral blood picture of a 26 year old male patient with chloroma in which nearly 85 per cent of the 40 000 leukocytes were typical chloroma cells (Courtesy of Professor H Morita)

Plate 61 Chloroleukemia





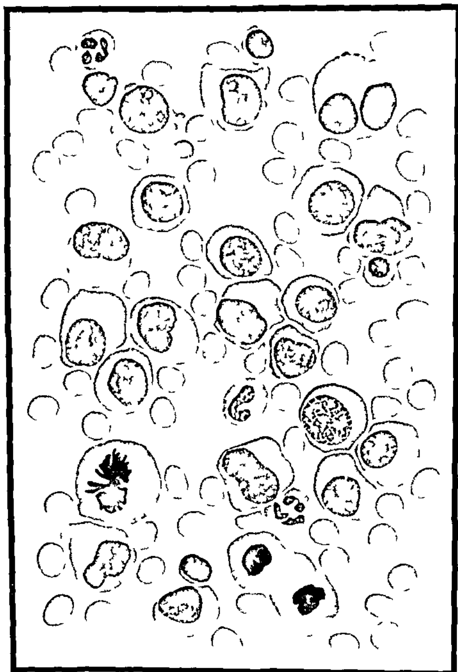
Cl Chloroma cell
mCl Myeloblastic chloroma cell
nMt Neutrophilic metamyelocyte
pNb Polychromatophilic normoblast
L Lymphocyte

Plate 61 shows the peripheral blood picture of a 26 year old male patient with chloroma in which nearly 85 per cent of the 10 000 leukocytes were typical chloroma cells (Courtesy of Professor H Morita)

PLATE 62

Chloroleukemia
(Iliac Myelogram)

Plate 62 Chloroleukemia (Iliac Myelogram)



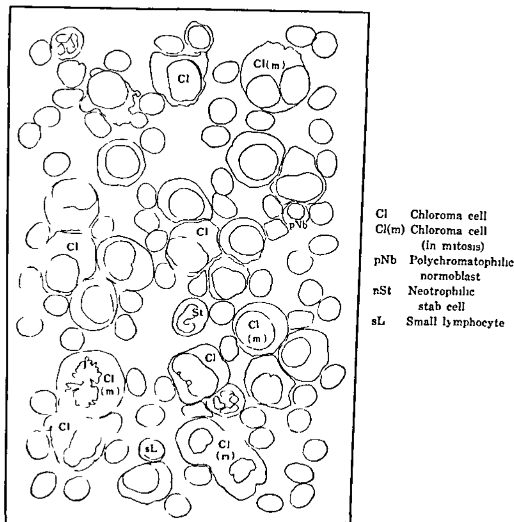
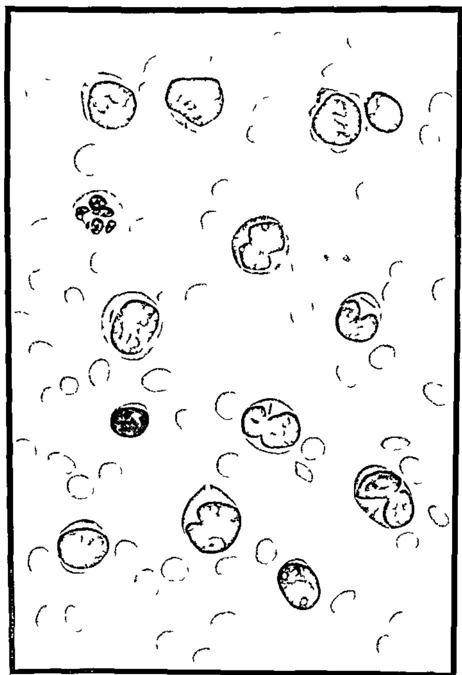


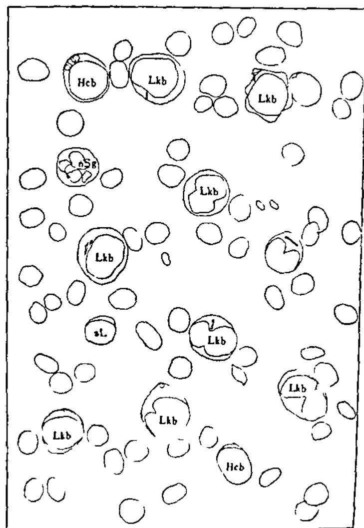
Plate 62 is a case of chloroma in a 25 year old patient showing a marked proliferation of chloroma cells in the iliac marrow (Courtesy of Dr S Manabe)

PLATE 63

Auer Bodies in Chloroleukemia

Plate 63 Auer Bodies in Chloroleukemia





Hcb Hemocytoblast
Lkb Leukoblast
sL Small lymphocyte
nSg Neutrophilic segmentocyte

Plate 63 depicts Auer bodies in the myeloblasts from a patient with chloro-leukemia

34 MONOCYTIC LEUKEMIA

Monocytic or histiomonocytic leukemia is accepted to be a distinct type of blood disorder clinically characterized by an acute febrile course and hematologically typified by a peripheral leukocytosis of moderate degree due to the presence of monocytes and histiocytes in abnormal proportions The existence of this disease was not recognized until in 1913 Reschad and Schilling Torgau described a typical case and called it splenocytic leukemia Since then many other similar cases have been observed and the literature has been adequately reviewed by several workers (Dameshek Clough Levine Doan and Wiseman and others) Theoretically a chronic form of the disease should exist but its actual occurrence is extremely rare or perhaps nonexistent

Clinically the disease runs a rapid course with necrotic involvement of the oral mucous membranes accompanied by hemorrhagic manifestations Purpura and frank bleeding may become persistent in the terminal stage The liver and spleen are usually enlarged but only to a moderate degree together with lymphadenopathy Recurrent bouts of fever often of the Pel Ebstein type and progressive weakness due to anemia are commonly experienced

The peripheral blood reveals both anemia and leukocytosis associated with a relative as well as an absolute increase of monocytes and histiocytes Great fluctuations in the leukocyte count may give rise to a subleukemic or even aleukemic picture While Downey (1938) recognized two varieties of acute monocytic leukemia the Schilling and Naegeli types only the first can be called a true histiomonocytic form since the pathognomonic cells seem to be derived directly from the reticuloendothelial system the second form is now generally designated as myelo monocytic leukemia for the blood picture is essentially that of myeloid leukemia associated with a remarkable monocytosis and the immature blast cells may well be either monoblasts or modified myeloblasts (so called paramyeloblasts) Thrombocytopenia often encountered in this disease may explain the development of hemorrhagic diathesis but these symptoms appear even in patients with definite thrombocytosis

The characteristic cells typifying this disease are definitely identified as monocytes in various stages of development Intermingled with these forms however there are always a number of large histiocytes having either an elongated tailed kitelike structure or a more oval shape The cytoplasm of these cells is bulky taking on a light blue tint and containing some fine dustlike granules while the nucleus is relatively small and provided with spongy chromatin By the supravital staining technic Dameshek (1930) noted these cells to have active motility sending out ameboid pseudopods and developing digestive vacuoles As a rule the nucleoli are inconspicuous

Pathologically a widespread hyperplasia of monocytoid and histiocytoid elements can be demon trated in the hemopoietic organs and connective tissue especially about the blood vessels the mode of proliferation appearing to be more diffuse in distribution than in other forms of leukemia The spleen liver lymph nodes and bone marrow present evidences of cellular hyperplasia mostly reticuloendothelial in nature

PLATE 64

Monocytic Leukemia
(Schilling Type)

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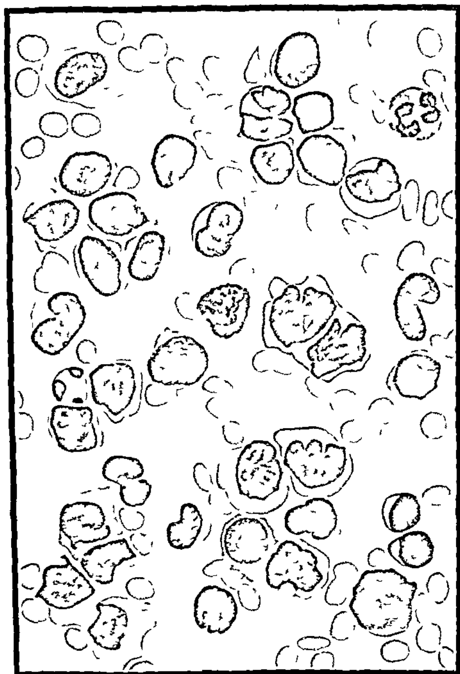
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Plate 64 Monocytic Leukemia (Schilling Type)



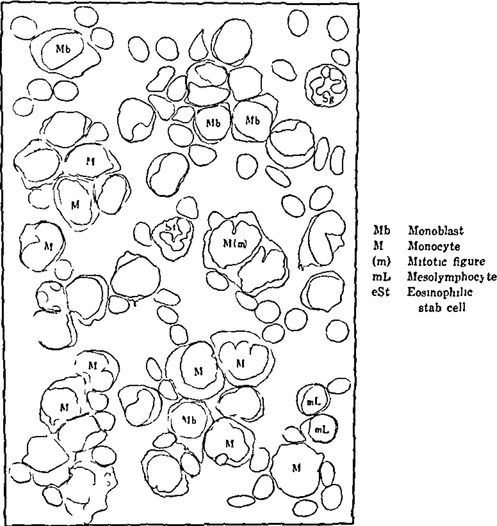
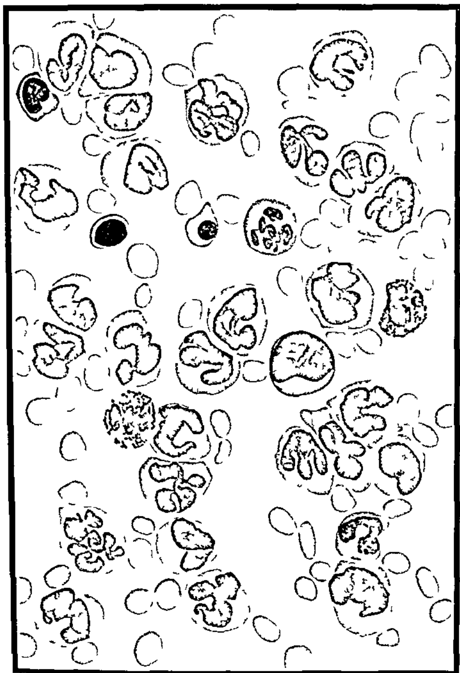


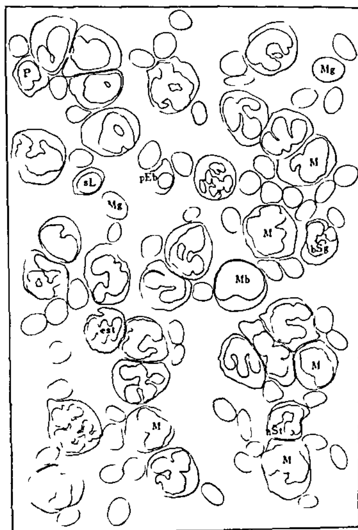
Plate 64 is monocytic leukemia (Schilling type) observed at the Mayo Clinic

PLATE 65

Monocytic Leukemia
(Naegeli Type)

Plate 65 Monocytic Leukemia (Naegeli Type)





Mb	Monoblast
M	Monocyte (paramyeloblast)
P	Plasmacyte
sL	Small lymphocyte
eSt	Eosinophilic stab cell
nSt	Neutrophilic stab cell
bSg	Basophilic segmentocyte
Mg	Megaloblast

Plate 65 is the peripheral blood in what is frequently called Naegeli type monocytic or myelomonocytic leukemia which however may be designated para myeloblastic leukemia

Plate 65 Monocytic Leukemia (Naegeli Type)

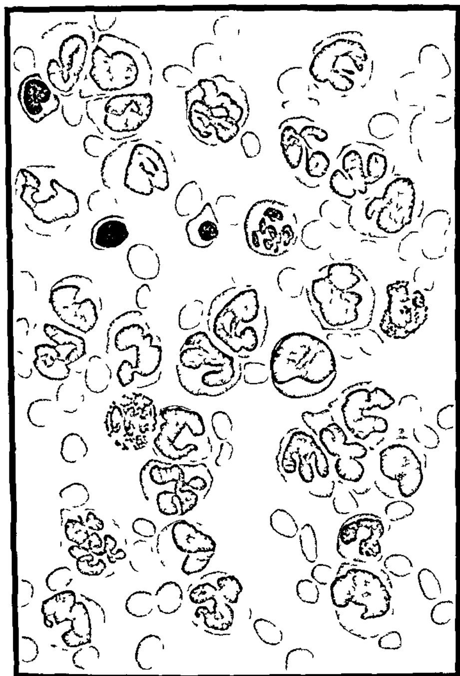


PLATE 66

Monocytic Leukemia
(Myelogram)

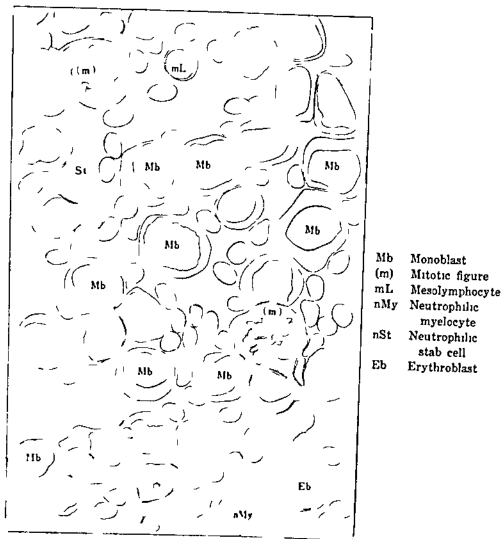


Plate 66 is the sternal marrow picture in acute monocytic leukemia (Courtesy of Dr E E Osgood)

Plate 66 Monocytic Leukemia (Myelogram)

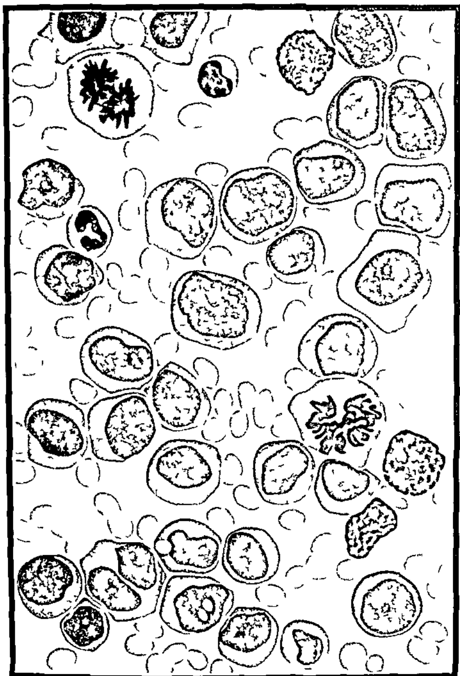
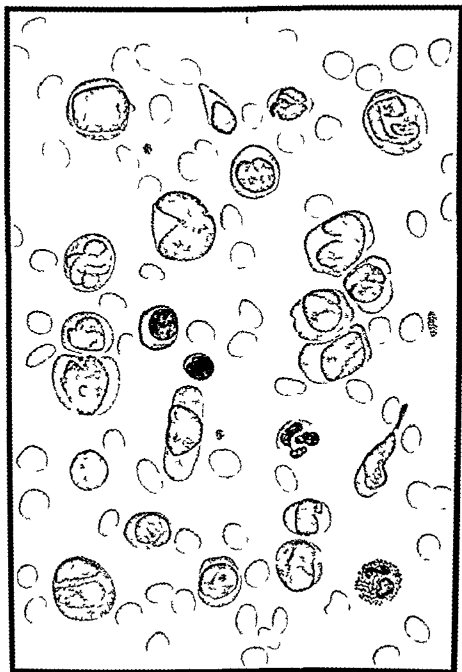


PLATE 67

Monocytic Leukemia

Plate 67 Monocytic Leukemia



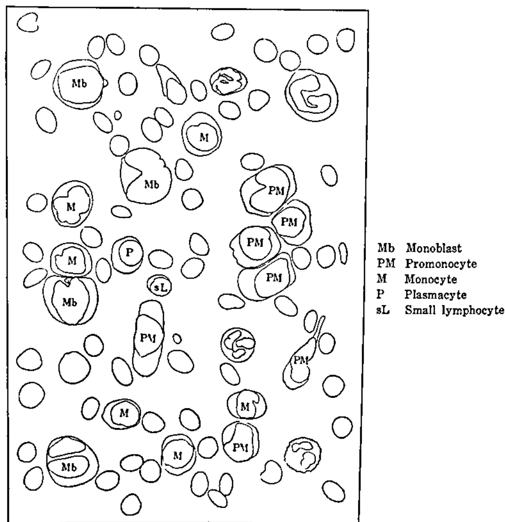


Plate 67 is the peripheral blood picture in monocytic leukemia

35 LEUKEMIC RETICULOENDOTHELIOSIS

Leukemic reticuloendotheliosis is a proliferative disease generally regarded as a type of reticulosis and characterized by an irreversible progressive hyperplasia of the reticuloendothelium wherever this element is normally prsent eventually producing leukemia The term was first used by Ewald (1923) in describing a case of acute leukemia in which the typical leukocytes were found to be extremely immature with abundant azurophilic granulation in the cytoplasm and the nucleus containing one to five distinct nucleoli These cells appeared to occupy an intermediate position between the reticuloendothelial cell and the hemocytoblast and to have been derived by budding from the reticulum cells of the splenic pulp liver sinusoids and bone marrow In this case the entire reticuloendothelial system was evidently stimulated producing a new type of cell either monocytoid or histiocytoid in nature It is known that proliferative activity of the reticuloendothelial system may result in formation of any type of blood cells sometimes in leukemic proportions However Letterer (1924) under the term aleukemic reticulosis described a condition characterized by generalized systemic hyperplasia of the vascular endothelium especially located in the hemopoietic organs but without any suggestions of leukemia in the peripheral blood Jaffe (1938) stated that reticuloendotheliosis reticulosis aleukemic reticuloendotheliosis and systemic hyperplasia of the reticuloendothelial cells of the blood forming organs are very different from each other the only link being a more or less systemic hyperplasia without apparent cause either of the reticuloendothelial cells or only one of its component elements

Available evidences indicate that the term leukemic reticuloendotheliosis should be used to denote the pathologic state characterized by a neoplastic process In clinical medicine it seems appropriate not to employ this name as a diagnostic designation inasmuch as the development of blood cells from the reticulum or even the increase of these cells in the blood does not necessarily mean leukemia The reaction may be only leukemoid in nature whatever the primary cause

Clinically the disease runs a rapid course accompanied by high fever severe anemia splenomegaly lymphadenopathy ulceration of the oral cavity and hemorrhagic diathesis all being classic signs of acute leukemia

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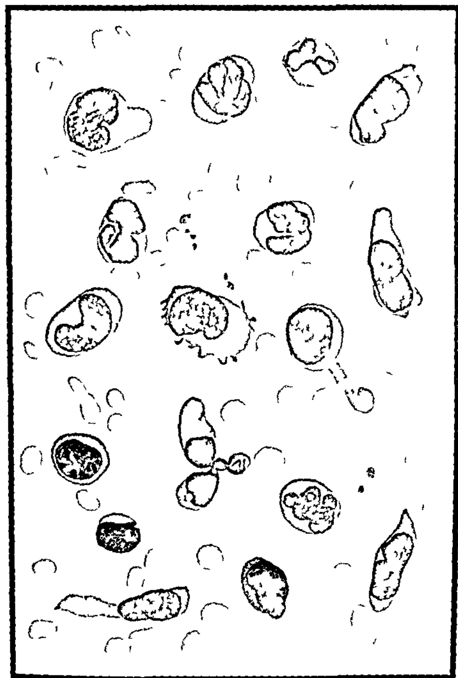
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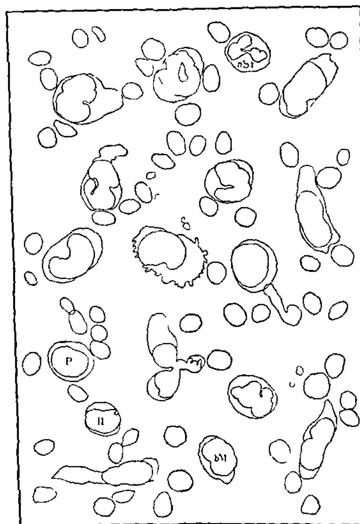
PLATE 68

Leukemic Reticuloendotheliosis

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Plate 68 Leukemic Reticuloendotheliosis

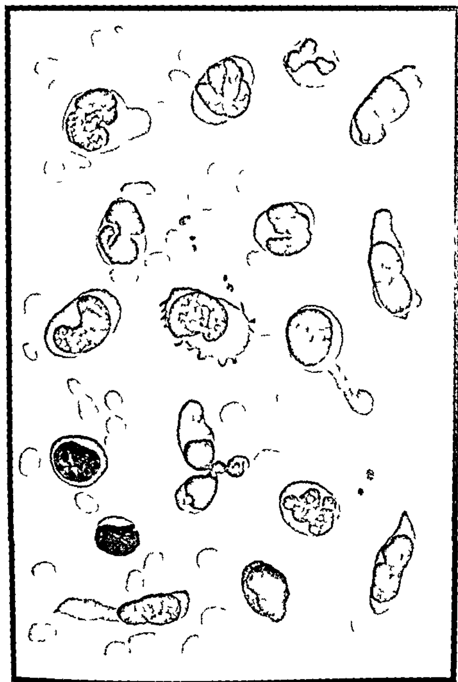




P Plasmacyte
lL Large lymphocyte
bMy Basophilic myelocyte
nSt Neutrophilic stab cell

Plate 68 is a case of leukemic reticuloendotheliosis seen in an infant 8 months in age with severe allergic manifestations

Plate 68 Leukemic Reticuloendotheliosis



36 INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis is an acute infectious disease benign in nature and probably caused by either viral or rickettsial infection It is clinically manifested by irregular fever sore throat cervical lymphadenopathy splenic enlargement and characterized by the appearance of atypical but mature lymphocytes in large numbers The first description of this disease was given in 1889 by Pfeiffer who called it glandular fever and many additional cases occurring in both epidemic and sporadic forms have since been reported Sprunt and Evans (1920) renamed this condition infectious mononucleosis while others have proposed such synonyms as acute benign lymphoblastosis acute lymphadenosis monocytic angina and lymphocytic angina While no definite microorganism has been universally accepted as being the causative agent the isolation of *Listerella monocytogenes* (Nyfeldt 1932) and of *Rickettsia sennetsu* (Misao and Kobayashi 1957) from patients with this disease appears to be most significant

After an incubation period of about 11 12 days the first symptom sore throat appears accompanied by fever headache and generalized malaise Lymphadenopathy mostly in the neck but also involving the nodes in other locations is characteristic The spleen and liver may also be enlarged Symptoms referrable to the cardiorenal pulmonary cutaneous and nervous systems may appear Hemorrhagic manifestations have also been noted

Hematologically the most characteristic feature is the appearance in the blood of atypical or leukocytoid lymphocytes which have been classified into three types by Downey and McKinlay (1923) The most frequently occurring cells belong to Type I which closely resemble normal large lymphocytes possessing a nucleus of varying configurations and a light blue cytoplasm with strands of darker blue material irregularly distributed The nucleoli are hardly discernible Type II cells appear somewhat immature and slightly larger in size and the nuclear chromatin is less condensed and the cytoplasm more homogeneous Type III cells are probably the most immature forms provided with chromatin granules of fine sievelike arrangement and basophilic cytoplasm closely simulating lymphoblasts in morphologic characteristics

The development of agglutinins against sheep red cells in high titers in the serum of patients with infectious mononucleosis discovered accidentally by Paul and Bunnell (1932) is of great value in the identification of this disease These antibodies are heterophilic in nature since they may be produced by an antigen quite unrelated to the etiologic agent The agglutinin titer is determined by the highest dilution showing a positive result in a set of 11 tubes containing serial dilutions of the patient s inactivated serum mixed with sheep red cells after standing for 2 hours at room temperature According to Davidsohn (1938) this reaction is nonspecific and the positive test is interpreted only as a presumptive index while the differential test decides the diagnosis by excluding the effect of Forssman antibody which is absorbed by the mashed guinea pig kidney suspension

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PLATE 69

Infectious Mononucleosis
(Type I)

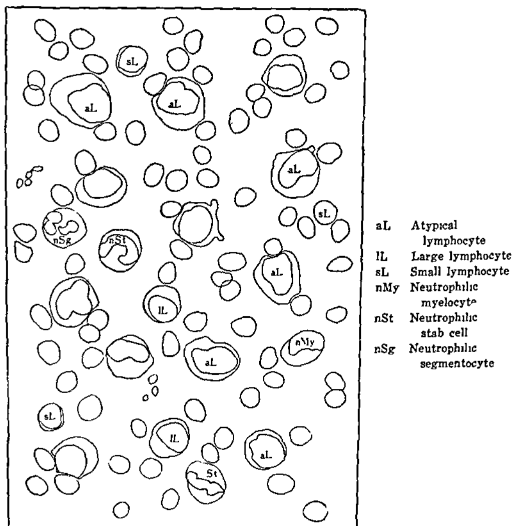


Plate 69 is infectious mononucleosis (Type I atypical lymphocytes)

Plate 69 Infectious Mononucleosis (Type I)

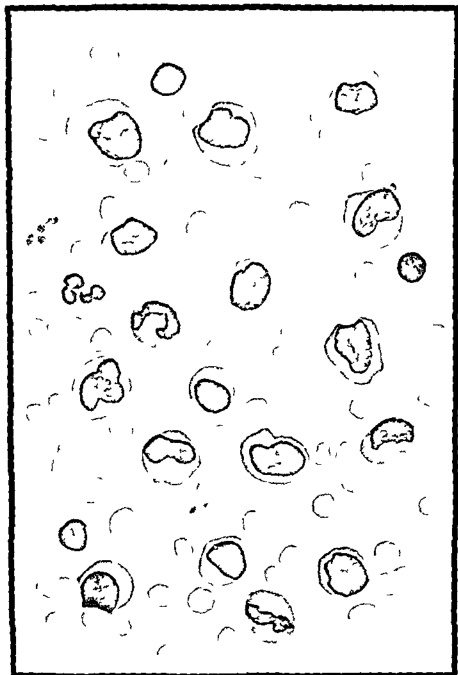
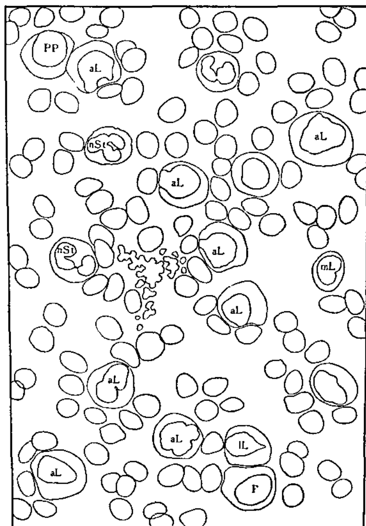


PLATE 70

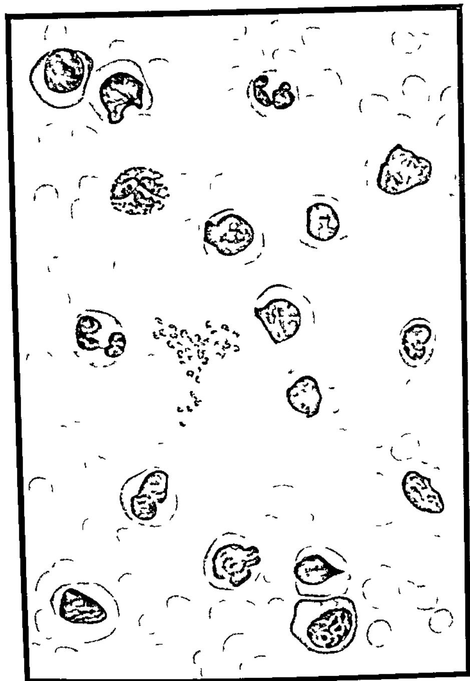
Infectious Mononucleosis
(Type II)



PP Proplasmacyte
P Plasmacyte
aL Atypical lymphocyte
lL Large lymphocyte
mL Mesolymphocyte
bSt Basophilic stab cell

Plate 70 is infectious mononucleosis (Type II atypical lymphocytes)

Plate 70 Infectious Mononucleosis (Type II)



37 PLASMA CELL LEUKEMIA

Plasma cell or plasmacytic leukemia is recognized as a specific blood disease manifested by symptoms common to all acute leukemic states and hematologically characterized by a high percentage of plasma cells present in the blood This condition while the plasma cells are abnormally proliferating in the bone marrow is frequently associated with extraosseous plasmacytomata in the lymph nodes (lymphadenosis leukemica plasmacellularis) In exceptional cases however Newman and his associates (1952) found no discrete tumor nodules by roentgenography or at autopsy In the first case reported by Foa (1902) the disease was called pseudoleukemia plasmocellularis and the pathognomonic cells were seen in the blood together with diffuse infiltration into various organs The term malignant plasmoma (Jores and Bruns) is sometimes used as a synonym for this disease

Like any acute leukemia the early symptoms of plasma cell leukemia are lassitude weakness weight loss and pain often accompanied by progressive anemia and tendency to hemorrhage Systemic involvement of practically all hemopoietic organs by plasma cell hyperplasia leads to splenomegaly hepatomegaly and lymphadenopathy The changes in the pancreas and kidneys may give rise to disturbances in the physiology of these organs

Laboratory studies reveal the presence of leukocytosis generally in which great numbers (30-90 per cent) or plasma cells are characteristic in company with severe anemia and thrombocytopenia Hyperproteinemia particularly hyperglobulinemia is usually demonstrated but the identification of Bence Jones bodies is not as conclusive as in multiple myeloma

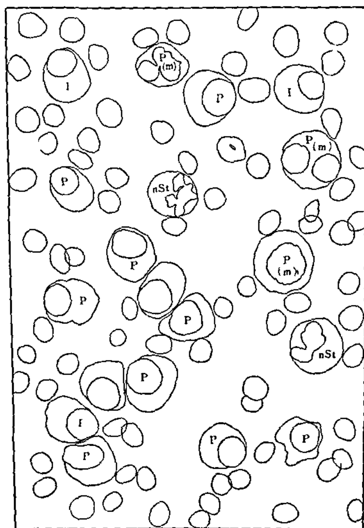
The morphologic features by which the plasma cell is differentiated from the so-called myeloma cell comprise cytoplasmic as well as nuclear peculiarities When fully matured the cytoplasm appears coarsely granular taking on a brilliant ultramarine hue but becomes rather transparent to form a narrow cream colored zone immediately surrounding the nucleus The chromatin material of the nucleus is clumped into heavy strands and assumes a cart wheel pattern in arrangement The nucleus itself is often seen eccentrically placed and hardly any visible nucleoli can be identified The immature forms such as plasmablasts and proplasmacytes are recognized by their more leptochromatic chromatin which shows little tendency to clump into bars while the cytoplasm is finely rather than coarsely granular In plasma cell leukemia the cells with these characteristics are greatly increased in the peripheral blood both relatively and absolutely In multiple myeloma however the blood usually shows an aleukemic picture

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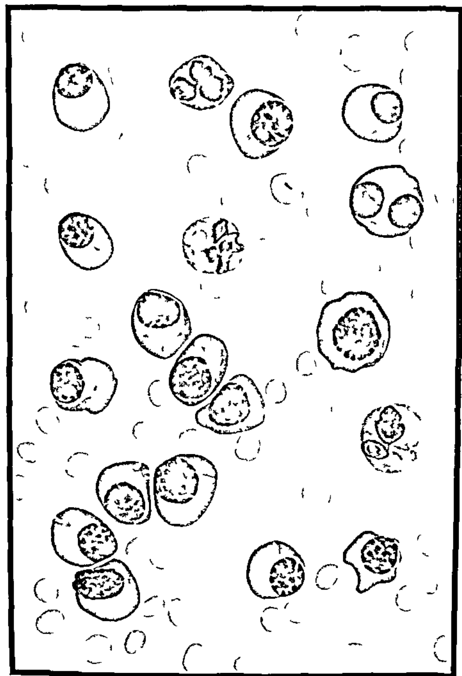
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P Plasmacyte
P(m) Plasmacyte (in mitosis)
nSt Neutrophilic stab cell

Plate 71 shows plasma cell leukemia in a 49 year old male patient reported by E. E. Osgood and W. C. Hunter. The peripheral leukocyte counts varied from 34 000 to 22 000 of which plasma cells occupied over 50 per cent and Turk cells 10 per cent. (Courtesy of the authors.)

Plate 71 Plasma Cell Leukemia



38 MULTIPLE MYELOMA

Multiple myeloma is a neoplastic disease of the bone marrow at first localized but eventually involving the entire skeletal system It is caused by a proliferation of myeloma cells inducing destructive lesions of the bone and is clinically manifested by pain pathologic fractures and progressive anemia The unusual feature of the disease is the accumulation in the blood and excretion in the urine of a peculiar protein perhaps an albumose known as Bence Jones protein Since the early observations made by McIntyre and others in 1845 and the occurrence of a new substance in the urine reported by Bence Jones in 1848 numerous case reports have appeared in the literature which have been summarized by Geschikter and Copeland (1928) The synonymous use of such designations as chronic plasmocytic leukemia aleukemic plasmocytoma or Kahler s disease (as an eponym) should be discouraged

Beginning as it does as a localized lesion the onset of the disease is insidious and the definitely recognizable symptoms of pain in the back anemia and uremia arthritic involvement epistaxis and pathologic fractures producing deformities with neurologic manifestations do not arise until the changes spread to multiple locations On the roentgenogram the lesions appear as areas of osteolysis usually roundish and punched-out in shape In a few instances the myelomatous changes may be seen only in the form of diffuse osteoporosis

Anemia of multiple myeloma is progressive but normocytic in type and the red cells exhibit a tendency to agglutinate readily with rouleaux formation This phenomenon arises under the influence of hyperproteinemia due to the increased production of γ globulin and cryoglobulin What has been called Bence Jones protein is considered to be not a single substance but a group of proteins At any rate the demonstration of this protein by its precipitation at temperatures between 10 and 60 C and its dissolution on cooling is still regarded to be diagnostically important According to the predominating protein multiple myeloma has been classified into α β_1 β γ (Wuhrmann and Wunderly) and perhaps M types (Gutman et al)

The leukocyte picture is within the normal range although a few plasma cells as well as small myeloma cells may occasionally be found in the peripheral blood but never in leukemic magnitude Lymphocytes and eosinophils may be relatively increased

The most outstanding feature in the histology of multiple myeloma is the predominance of myeloma cells in the hemopoietic areas The classic myeloma cell is large 15–20 microns in diameter round or ovoid in shape and contains one or more spherical or egg shaped nuclei There is no tendency to form strands or bars on the part of the leptochromatic substance of the nucleus but instead there are usually a few aggregations of somewhat densely stained chromatin Unlike in the plasma cell the nuclear chromatin of the myeloma cell lacks any suggestion of cart wheel arrangement The cytoplasm is made up of almost homogeneous or finely granular material and takes on a muddy blue stain occasionally containing a few small vacuoles and a urophilic dusts The myeloma cell can be differentiated from the plasma cell by specific stains such as the methyl green pyronine method of Unna Pappenheim The question as to whether the myeloma cell originates from the blood cell or from some other constituent of the bone marrow particularly the osteoclast has not been completely settled

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PLATE 72

Multiple Myeloma
(Myelogram)

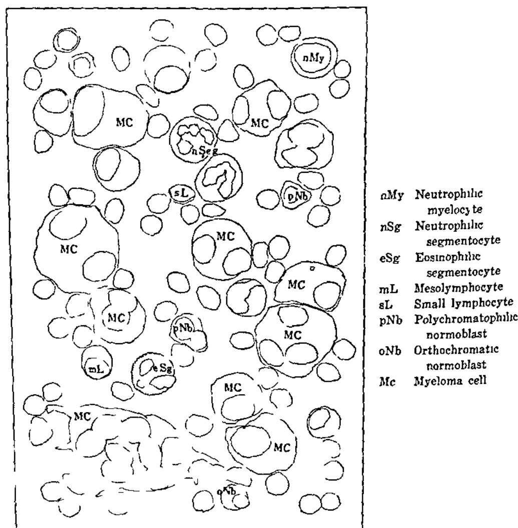
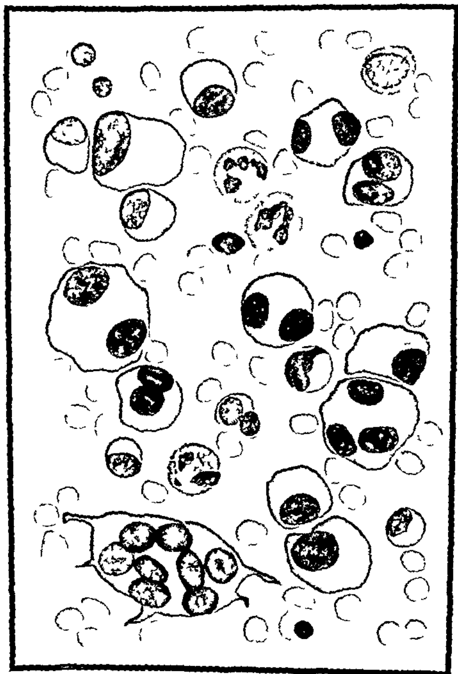


Plate 72 represents the concentrated bone marrow picture from a male patient age 57 with the diagnosis of multiple myeloma and suffering from generalized bone lesions (Courtesy of Drs H Downey and Dorothy Sundberg)

Plate 72 Multiple Myeloma (Myelogram)



39 SEX CHROMATIN (DRUMSTICK)

In 1954 Davidson and Smith first proposed the existence of the sexual dimorphism of leukocytes by demonstrating the distinction between the male and female characteristics in the nuclear configuration of mature polymorpho nuclear neutrocytes This differentiation is based essentially on the presence or absence of drumsticks protruding out from the nuclear lobes as stalked or sessile rounded appendages of chromatin measuring about 1 5 microns in diameter The presence of these drumsticks in any number is called chromatin positive and their absence chromatin negative It has been found that the chromatin sex is female in the former but is male in the latter the frequency occurrence varying from 20 to 80 per cent Although this statement generally holds certain exceptions must be recognized since the occurrence of a rare phenomenon of human chimerism has been reported by Booth et al (1957) and by Nicholas et al (1957)

Morphologically these extra chromatin pieces are classified into 4 types Type A is the classic type commonly seen as a hanging drop of deeply stained chromatin connected to a nuclear lobe by a single thin strand or bridge of the same material Type B includes both sessile nodules and tags of chromatin attached directly to the nucleus either on broad bases or tips Type C comprises intermediate varieties such as rod hook and thread forms occasionally all of these in one cell or even in the same cell accompanied by a drumstick or sessile nodule Type D is a ring form or one resembling a tennis racket connected to the nuclear membrane by a filament In pratice the total number of A and B is counted and a quotient A+B C is calculated Experience indicates a clear and unequivocal dichotomy at the level of 0 5 the values higher than this signify ing the females and those lower the males

The establishment of the concept of chromatin sex naturally leads to its diagnostic application in endocrinopathy and certain dysgenetic states such as ovarian agenesis (Turner s syndrome) primary testicular agenesis (Klinefelter s syndrome) adrenogenital syndrome and testicular feminization Briggs and Kupperman (1956) have demonstrated the usefulness of chromatin sex deter mination in the management of intersex and in assaying the reproductive pro gnosis in infants of intermediate sex

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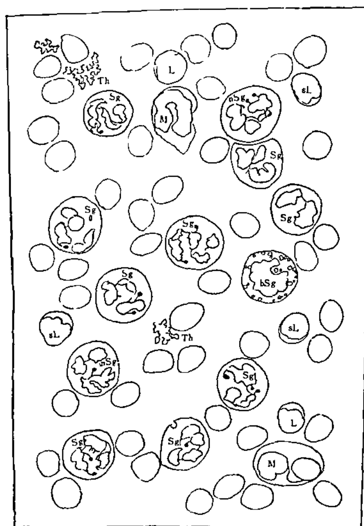
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PLATE 73

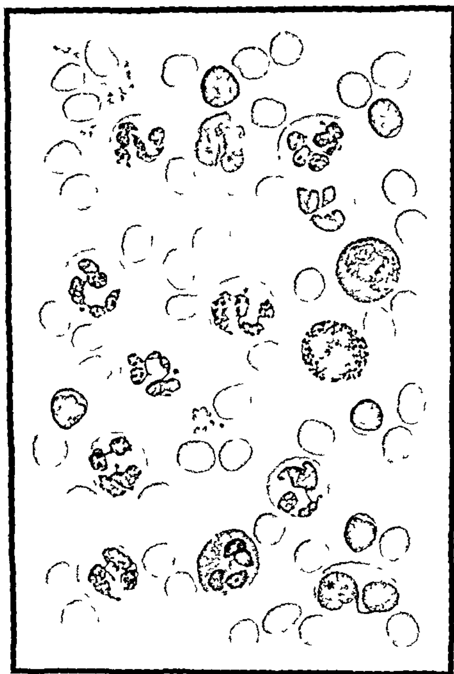
Sex Chromatin (Drumstick)



nSg	Neutrophilic segmentocyte (drumsticks)
bSg	Basophilic segmentocyte
M	Monocyte
sL	Small lymphocyte
Th	Thrombocyte

Plate 73 shows drumsticks on the lobes of polymorphonuclear neutrophils in a female (Courtesy of Drs M Hayakawa and A Tanaka)

Plate 73 Sex Chromatin (Drumstick)



40 LEUKOERYTHROBLASTOSIS

This term is applied by Wintrobe to the type of anemia associated with space occupying disorders of the bone marrow characterized by the presence in the circulating blood of immature leukocytes of the myeloid series as well as nucleated red cells sometimes in great numbers Since the bone marrow is the principal site of involvement and yet early polycythemia may be found such synonyms as myelophthisic anemia and leukocrythroblastic anemia (Vaughan) have been suggested This condition is often seen in bone marrow metastasis of carcinoma and in myelofibrosis or myelosclerosis the latter being characterized by marked splenomegaly and extremely chronic course Depending upon the particular aspect of the etiology or pathology of this disease emphasized by various observers many confusing names have appeared in the literature some of which may belong to the same category These include aleukemic mega karyocytic myelosis myeloid megakaryocytic hepatosplenomegaly chronic non leukemic myelosis and even agnogenic myeloid metaplasia The features common to all of these cases are according to Wintrobe the hypoplastic or hypofunction ing bone marrow splenomegaly the presence of immature red and white cells in the blood and myeloid metaplasia in the liver and spleen This type of anemia may also be encountered in marble bone disease or osteopetrosis (Albers Schonberg) as well as in primary xanthomatoses (Gauchers disease Niemann Picks disease Schuller Christians disease) in which the bone marrow is ex tensively invaded by lipoid laden macrophages

The symptoms vary according to the nature of the underlying disease but the striking splenomegaly calls for differential diagnosis with special reference to the disturbances of the hemopoietic organs Pressure pain in the abdomen deep bone pain epistaxis and purpura accompanied by weakness and loss of weight are rather common Complicating infections must also be looked for

The hematologic picture conforms to no standard variation the number of red cells as well as that of white cells being either decreased or increased The presence of normoblasts increase in reticulocytes poikilocytosis and even occa sional finding of stippled cells and Cabot rings have been reported While thrombocytopenia is a rule some exceptional cases may show an abnormal proliferation of megakaryocytes with resulting thrombocytosis in the bone marrow In the presence of myelosclerosis it may be difficult to obtain a satisfactory amount of marrow material by sternal aspiration and the bone may give a gritty feel on picture If the bone marrow is the site of carcinomatous metastasis specific tumor cells may be found in the sternal puncture

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PLATE 74

Leukoerythroblastosis
(Aleukemic Myelosis)

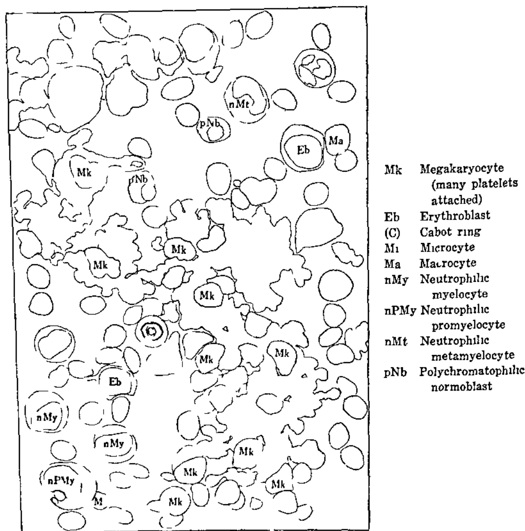
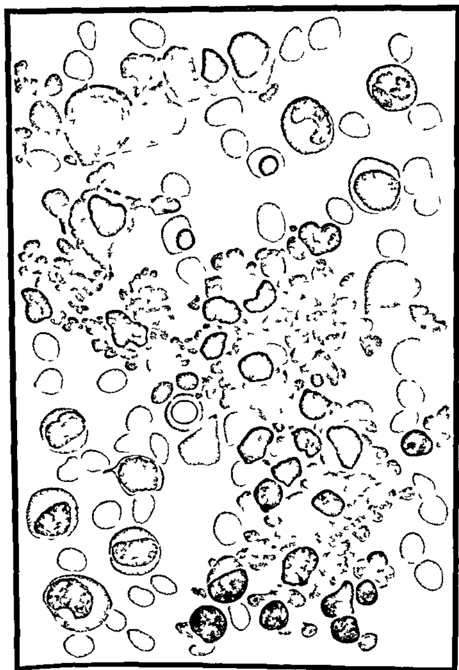
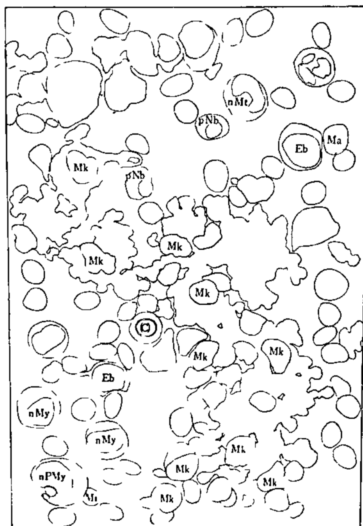


Plate 74 shows the sternal marrow picture of a 34 year old male patient with megakaryocytosis and atypical platelet production The peripheral blood was characterized by a marked anemia associated with leukemoid reaction The bones revealed marked changes due to striking osteosclerosis (Reported by G Carpenter and C M Flory)

Plate 74 Leukoerythroblastosis (Aleukemic Myelosis)





Mk	Megakaryocyte (many platelets attached)
Eb	Erythroblast
(C)	Cabot ring
Mi	Microcyte
Ma	Macrocyte
nMy	Neutrophilic myelocyte
nPMy	Neutrophilic promyelocyte
nMt	Neutrophilic metamyelocyte
pNb	Polychromatophilic normoblast

Plate 74 shows the sternal marrow picture of a 34 year old male patient with megakaryocytosis and atypical platelet production The peripheral blood was characterized by a marked anemia associated with leukemoid reaction The bones revealed marked changes due to striking osteosclerosis (Reported by G Carpenter and C M Flory)

41 NEUTROPHILIA

Neutrophilia designates a state of peripheral leukocytosis in which the absolute number of neutrophilic granulocytes is increased above the accepted normal level In cases of leukopenia even though the proportion of neutrophils may be increased the total number is either normal or subnormal a condition generally called relative neutrophilia The etiologic factors of absolute neutrophilia include acute bacterial infections intoxications metabolic disturbances acute blood loss sudden hemolysis and stress stimuli of various types Neutrophilia represents a definite phase of the defense mechanism of the living body its peak coinciding roughly with the maximal stage of causative influence and gradually returning to the normal level with the subsidence of the stimulus In addition to the well known phagocytic power of granulocytes the neutrophils particularly have received most intensive histochemical studies Wachstein (1946) demonstrated that both the number of the granulocytes giving positive Gomori reactions for alkaline phosphatase was greater and the strength of the reaction was more remarkable in infections than in chronic granulocytic leukemia While the exact significance of this and other chemical findings has not been entirely elucidated the constitution of neutrophilic granulocytes has an important bearing on the physiology of these cells

Morphologically all maturation forms participate in neutrophilia although the so-called juvenile forms myelocytes and metamyelocytes are involved to a limited extent In leukemoid reactions characterized by neutrophilia even the appearance of a few myeloblasts has been noted In the majority of cases the participation of staff cells or rhabdocytes is most conspicuous while the increase in number of polymorphonuclear cells or segmentocytes may be relatively less remarkable For the purpose of evaluating the significance of neutrophilia in clinical practice numerous systems of differential counting (hemogram) have been evolved Thus Arneth (1904) divided the neutrophils into five classes according to the shape and number of their nuclei designating the increase of the immature forms as a shift to the left and that of the mature varieties as a shift to the right A more simplified but similar classification has been offered by Schilling (1911)

The qualitative changes in the cytoplasm of neutrophils have been studied by numerous observers and aside from the chemical abnormalities in the variation of alkaline phosphatase glycogen content lipids and others the presence and physiology of certain enzymes have also been investigated The appearance of so-called toxic granules in the neutrophilic cytoplasm has for a long time been regarded as predicting an unfavorable prognosis quite contrary to actual experience The degree and extent of toxic granulation however appear to be inversely related to the enzyme content as determined by peroxidase reactions While it is reasonable to consider the presence of toxic granules as definitely abnormal these changes are not necessarily manifestations of cell damage but merely expressions of temporary influence

PLATE 75

Neutrophilia

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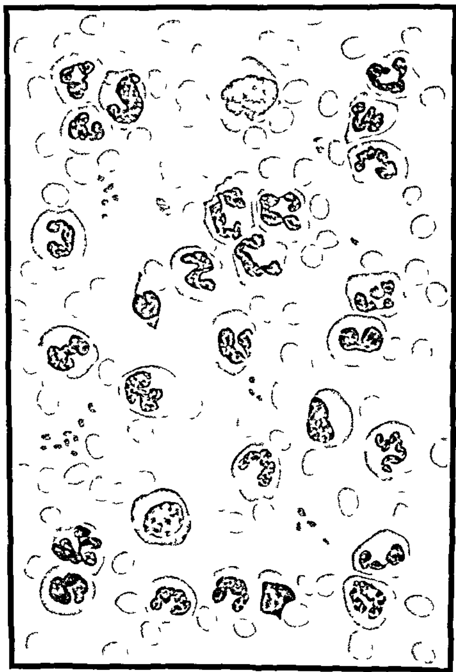
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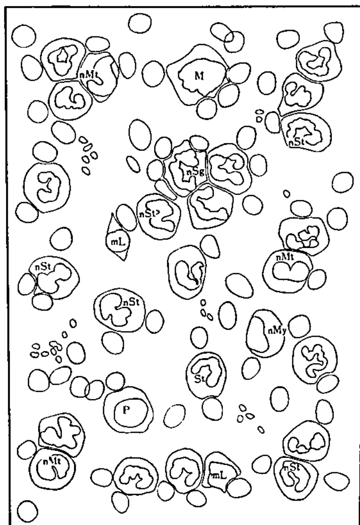
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Plate 75 Neutrophilia





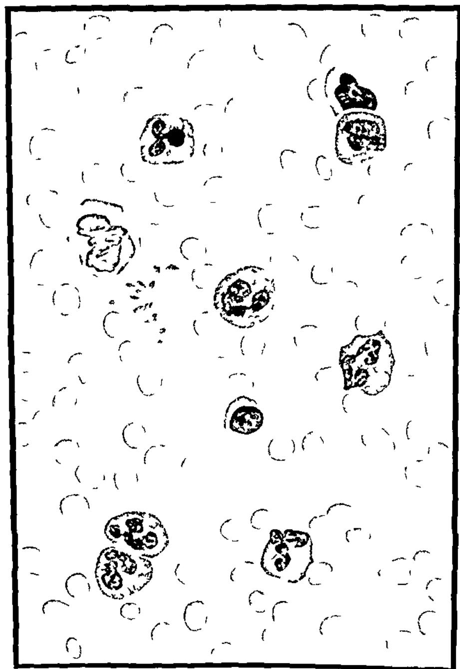
M Monocyte
mL Mesolymphocyte
P Plasmacyte
nMy Neutrophilic myelocyte
nMt Neutrophilic metamyelocyte
nSt Neutrophilic stab cell
nSg Neutrophilic segmentocyte

Plate 75 is a case of marked leukocytosis (56 000) with a pronounced shift to the left in a 53 year old male patient suffering from cellulitis and erysipelas of the right leg during the stage of high fever (Courtesy of the Mayo Clinic)

PLATE 76

Toxic Granulation in Neutrophilia

Plate 76 Toxic Granulation in Neutrophilia



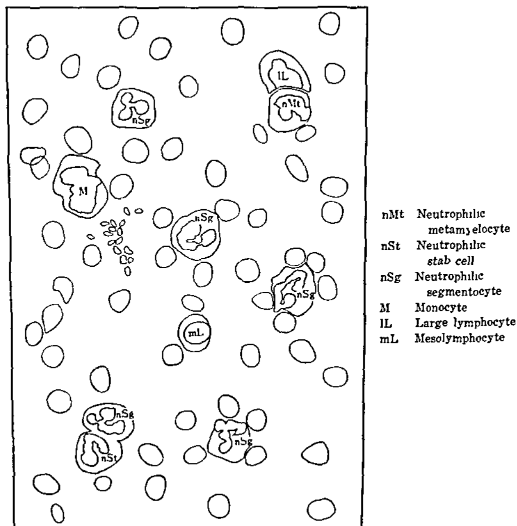
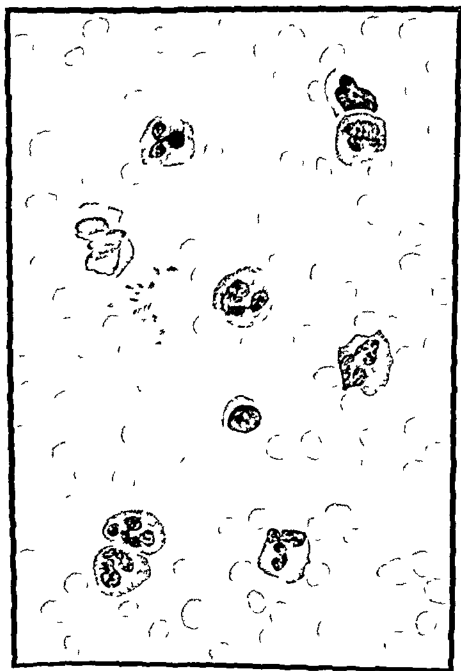


Plate 76 shows the presence of numerous toxic granules in the cytoplasm of polymorphonuclear neutrophils in a patient with chronic osteomyelitis of the lumbar vertebrae and right hip (Courtesy of the Mayo Clinic)

Plate 76 Toxic Granulation in Neutrophilia



42 GRANULOCYTOPENIA AND AGRANULOCYTOSIS

Agranulocytosis is a syndrome consisting of severe sore throat marked prostration and extreme reduction or even complete disappearance of granulocytes from the peripheral blood followed by sepsis and fatal termination. Although the condition was described by Werner Schultz (1922) as a distinct disease similar cases had previously been observed by Brown (1902) and Turk (1909). While the etiology is not entirely known Kracke (1931) showed that the mounting incidence of this disease coincided with the widespread use of certain coal tar derivatives particularly those containing a modified benzene ring. This possible relationship was confirmed by Madison and Squire (1934) on clinical grounds. Numerous synonyms used for this disease include agranulocytic angina agranulosis agranulocythemia malignant or pernicious leukopenia and many others. The conditions designated by such names as granulopenia hypogranulocytosis granulocytic hypoplasia and the like are merely descriptive of a decrease in the number of granulocytes and should be distinguished from the disease entity here concerned.

The disease is ushered in with sudden onset marked by chills and hyperpyrexia associated with necrotizing angina and gangrenous ulceration of the mucous membranes throughout the body. Due to the extreme leukopenia the resistance against invading microorganisms is reduced to the utmost so that practically all tissues serve as media for the pure culture of bacteria setting up multiple foci of infection and septic infarcts in many organs. The course of the disease being so rapid there is little time to produce splenomegaly or lymphadenopathy. Uncontrollable sepsis rapid pulse and extreme prostration characterize the terminal picture.

Hematologically the most unique feature is the development of alarming leukopenia with almost complete absence of granulocytes in the peripheral blood. A few granulocytes 1–2 per cent on differential count may be encountered in the entire smear preparation and these are grossly abnormal with pyknotic nuclei and often vacuolated cytoplasm which is provided with poorly stainable granules. There are few changes in the red cells and platelets are fairly normal. Hemorrhages occur as a result of blood vessel damage due to the extension of ulcerative processes from the neighboring mucous membrane. The bone marrow picture is characterized by a hyperplasia of immature myeloid cells with no tendency to proceed further in their maturation a condition often called granulocytic anakmesis. Some observers entertain the view that agranulocytosis results from the action of antigranulocytic agglutinins developing in the plasma of patients sensitive to the leukopenia inducing agents. In a case observed by Rosenthal and Abel (1936) there was a relative increase of monocytes and it was reported as monocytic agranulocytosis or leukopenic infectious mononucleosis.

Quite different from agranulocytosis is a group of rather ill defined cases characterized by chronic granulocytopenia including (1) periodic or cyclic neutropenia (2) primary splenic neutropenia (3) chronic hypoplastic neutropenia (4) chronic granulocytopenia of children and (5) familial neutropenia

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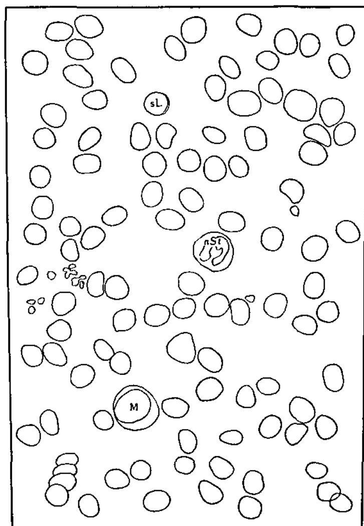
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PLATE 77

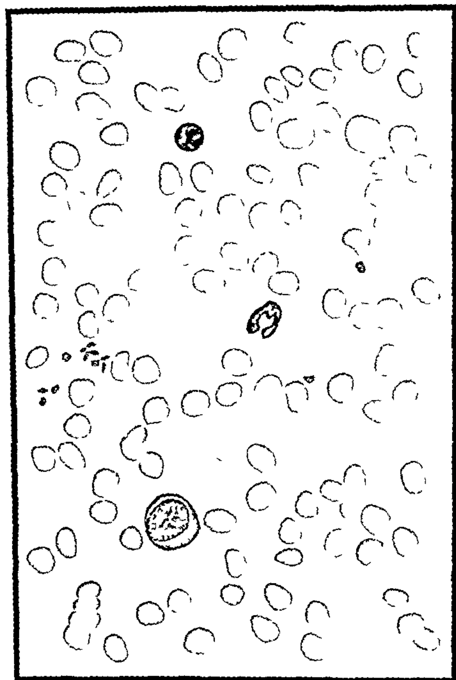
Agranulocytosis



sL Small lymphocyte
nSt Neutrophilic stab cell
M Monocyte

Plate 77 is agranulocytosis (Schultz) in a young patient

Plate 77 Agranulocytosis



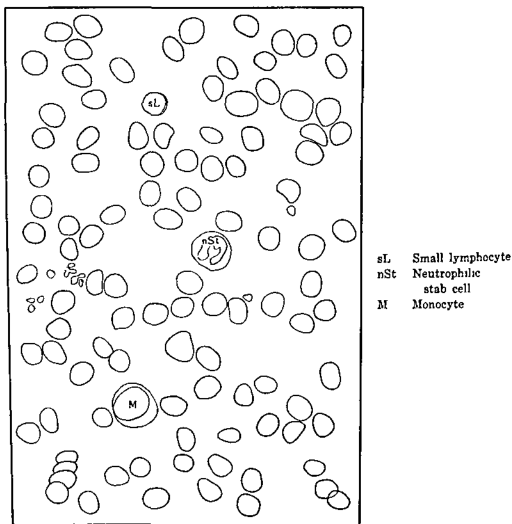
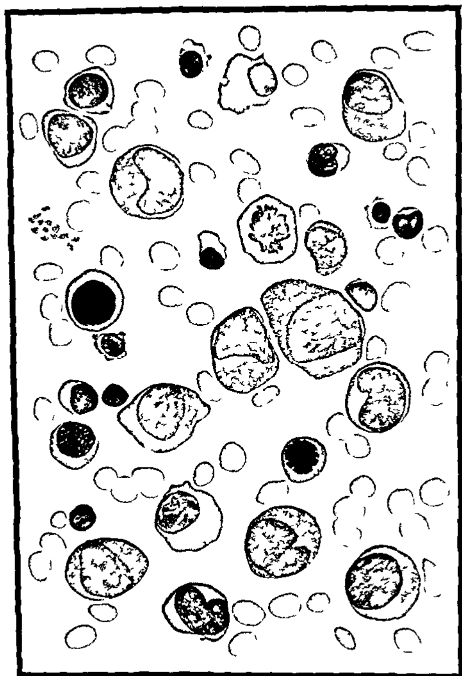


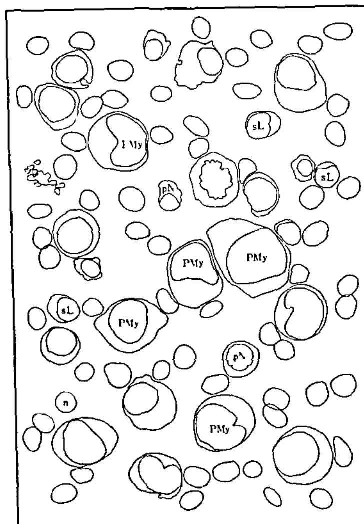
Plate 77 is agranulocytosis (Schultz) in a young patient

PLATE 78

Agranulocytosis
(Myelogram)

Plate 78 Agranulocytosis (Myelogram)





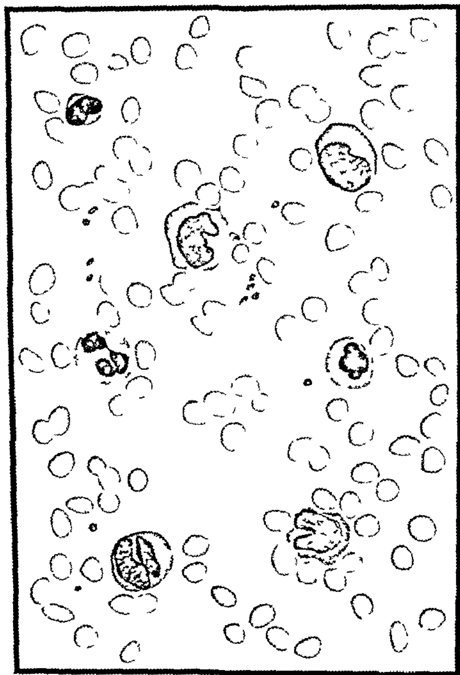
sL Small lymphocyte
pN Polychromatophilic normoblast
PMy Promyelocyte
(n) Free nucleus of normoblast

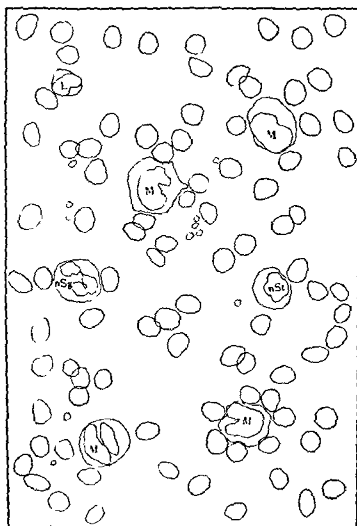
Plate 78 is the sternal marrow picture in agranulocytosis suggesting a possibility of maturation arrest of granulocytes

PLATE 79

Monocytic Agranulocytosis

Plate 79 Monocytic Agranulocytosis

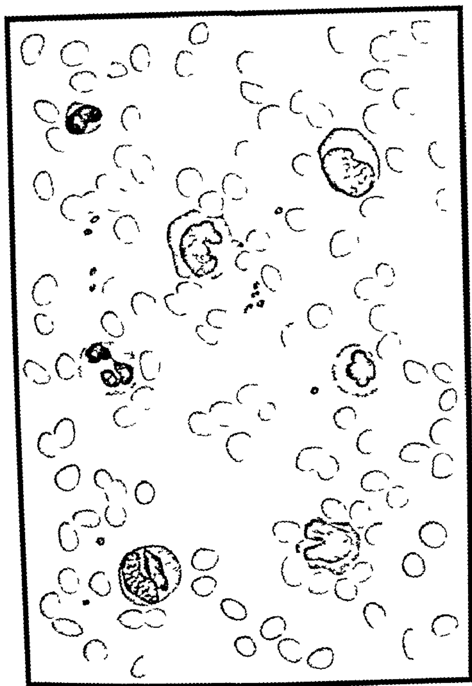




M	Monocyte
sL	Small lymphocyte
nSt	Neutrophilic stab cell
nSg	Neutrophilic segmentocyte

Plate 79 has been drawn from the peripheral blood smear made from a patient with *monocytic agranulocytosis* (leukopenic *infectious monocytosis*) reported by Rosenthal and Abel (1936) who kindly furnished the material

Plate 79 Monocytic Agranulocytosis



43 LYMPHOCYTOSIS

Lymphocytosis refers to an increase above normal in the number of circulating lymphocytes under a variety of stimulations The increase may be absolute or relative permanent or temporary although the term is usually employed to designate a hematologic picture characterized by an absolute but transient increase of benign nature This blood finding is most frequently encountered in certain acute infections notably pertussis infectious mononucleosis and acute infectious lymphocytosis as well as in chronic infections such as tuberculosis during the quiescent stage secondary syphilis undulant fever and infectious hepatitis It may also occur during the convalescent stage of many infectious diseases and in thyrotoxicosis Physiologically the blood of infants and children during the first four years of age is typified by lymphocytosis Relative lymphocytosis as a counterpart of neutropenia or granulocytopenia may sometimes be striking but its clinical significance is not as great as that of absolute lymphocytosis

Morphologically any strain of lymphocytes may be concerned in producing lymphocytosis but the predominating strain appears to be constant in a given disease Thus the strain involved in pertussis is chiefly the small variety while that in infectious mononucleosis is usually the large type It is difficult to properly evaluate the exact significance of any particular type of lymphocytes appearing in increased numbers although the difference in the source of lymphopoietic origin as well as in the nature of stimuli may be an explanation Certain morphologic alterations of lymphocytes as related to endocrine stimuli often designated as stress lymphocytes have been observed consisting of nuclear and cytoplasmic distortion as compared with those under normal conditions While the lymphocytic hemogram (Reich 1933) and the Y (young) M (mature) O (old) relationship in diseases (Wiseman 1931) have not been extensively utilized there is ample evidence indicating that the qualitative as well as quantitative changes need to be more carefully evaluated than hitherto customary when confronted with lymphocytosis

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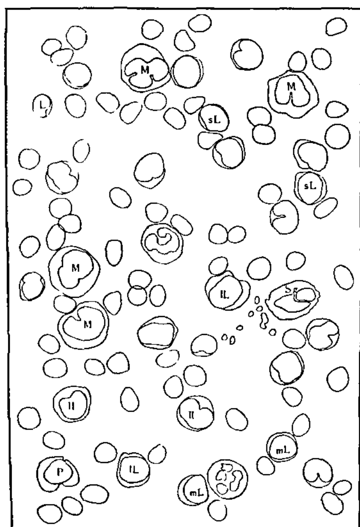
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PLATE 80

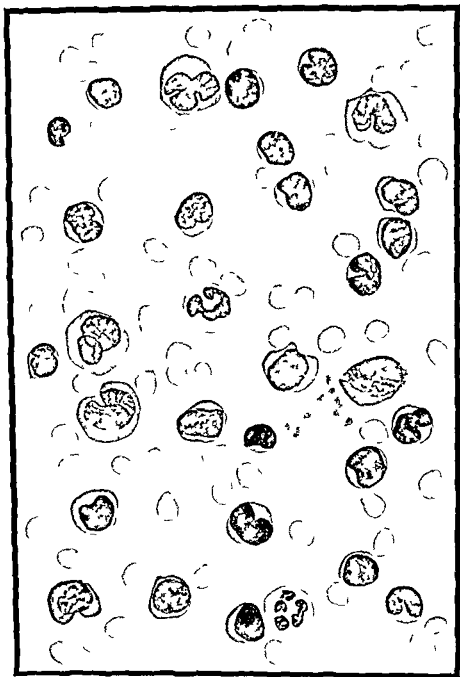
Lymphocytosis in Pertussis

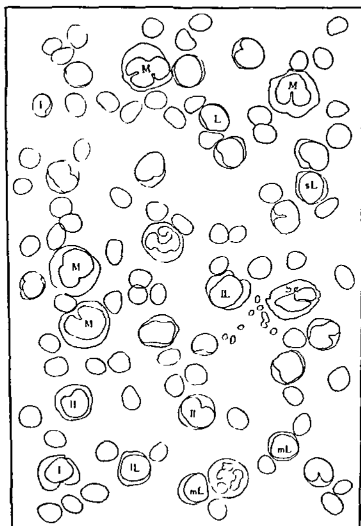


M	Monocyte
lL	Large lymphocyte
mL	Mesolymphocyte
sL	Small lymphocyte
eSg	Eosinophilic segmentocyte
P	Plasmacyte

Plate 80 is the blood picture in pertussis with a leukocytosis of 15 000 of which lymphocytes and monocytes were increased to 75 per cent and 4 per cent respectively

Plate 80 Lymphocytosis in Pertussis

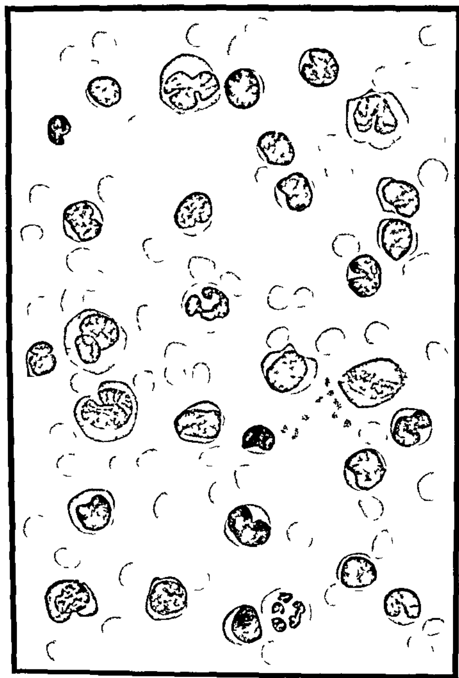


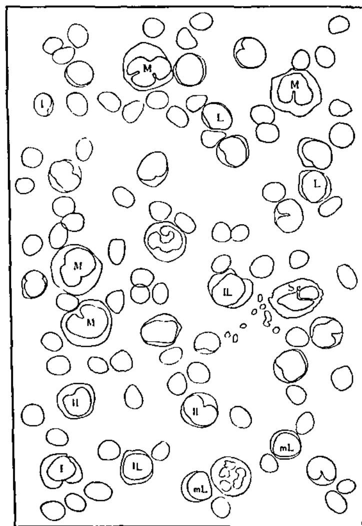


M	Monocyte
lL	Large lymphocyte
mL	Mesolymphocyte
sL	Small lymphocyte
eSg	Eosinophilic segmentocyte
P	Plasmacyte

Plate 80 is the blood picture in pertussis with a leukocytosis of 45 000 of which lymphocytes and monocytes were increased to 75 per cent and 1 per cent respectively

Plate 80 Lymphocytosis in Pertussis





M	Monocyte
lL	Large lymphocyte
mL	*Mesolymphocyte*
sL	Small lymphocyte
eSg	Eosinophilic segmentocyte
P	Plasmacyte

Plate 80 is the blood picture in pertussis with a leukocytosis of 15 000 of which lymphocytes and monocytes were increased to 75 per cent and 4 per cent respectively

44 VIROCYTES AND VIROLYMPHOCYTOSIS

Virolymphocytosis refers to a condition of the blood frequently encountered in some infectious diseases of viral origin or occasionally in certain allergic states characterized by the presence of an increased number of atypical or abnormal lymphocytes Since these atypical cells are frequently seen in infectious mononucleosis Downey and Stasney (1935) designated these as leukocytoid but Litwins and Liebowitz (1951) found these abnormal lymphocytes in many cases of virus disease other than infectious mononucleosis and preferred to call them virocytes More accurately however these cells may best be designated as virolymphocytes In 1923 Jones and Minot described a case of infectious or catarrhal jaundice in which the peripheral blood contained 50–60 per cent of atypical lymphocytes morphologically identical to the leukocytoid cells of Downey and co workers The present writer saw these cells in the blood of an infant suffering from roseola infantum while Moeschlin (1941) and later Siede (1948) encountered them in cases of primary atypical pneumonitis and herpes zoster (Siede 1949) Again Liebowitz and his associates (1949) observed the presence of these cells in the blood of a blood bank worker who developed serum hepatitis The appearance of these abnormal lymphocytes in allergic conditions was reported by Pandolph and Gibson (1944) and these cells may also be found in the blood of patients with nonviral infections such as undulant fever and rickettsial pox

Morphologically the virolymphocytes are essentially large lymphocytes with an abundant deeply basophilic cytoplasm which contains no specific or azurophilic granules The nucleus is relatively large and its chromatin is either fine and delicate or semipachychromatic often containing visible nucleoli Some of these cells closely resemble typical lymphoblasts and differentiation from lymphoblastic leukemia must be carefully made under these circumstances As a rule these abnormal lymphocytes gradually disappear from the blood during the recovery phase of the disease

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PLATE 81

Virolymphocytosis

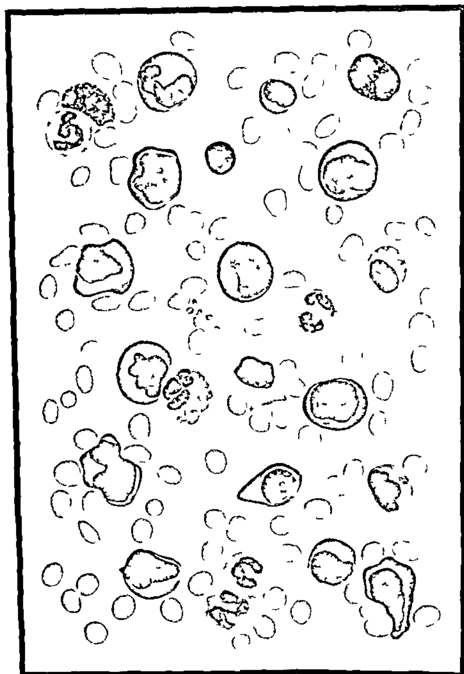
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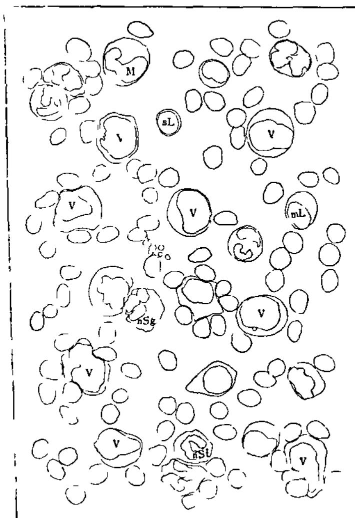
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Plate 81 Virolymphocytosis





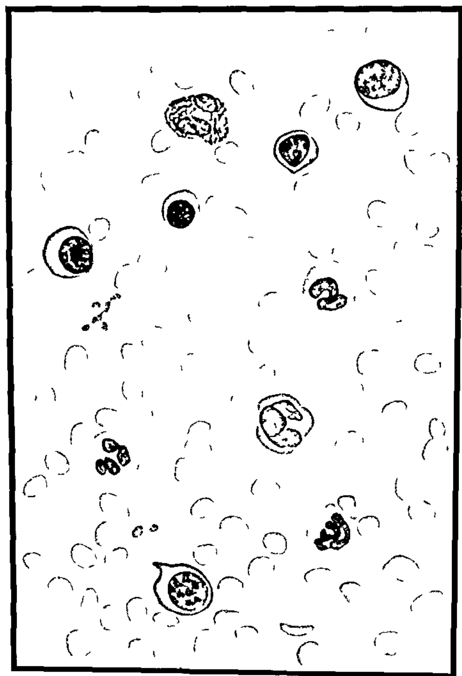
V	Virocyte
lL	Large lymphocyte
mL	Mesolymphocyte
sL	Small lymphocyte
nSt	Neutrophilic stab cell
nSg	Neutrophilic segmentocyte

Plate 81 shows the morphologic charatceristics of virolymphocytes (Courtesy of Dr K Sato)

PLATE 82

Virocytes in German Measles

Plate 82 Virocytes in German Measles



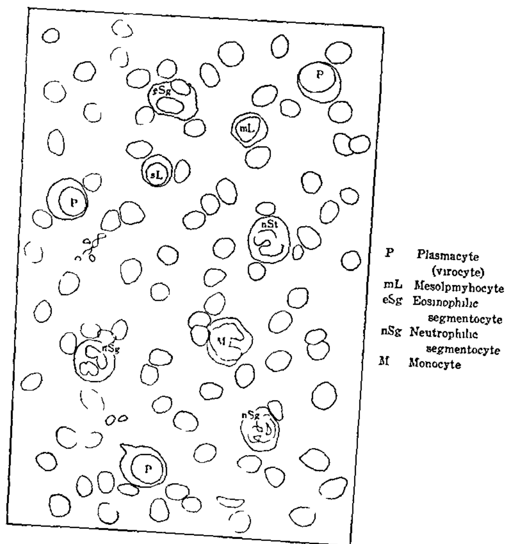


Plate 82 shows the peripheral blood picture in an infant with German measles in which many virocytes closely resembling plasma cells are present

45 ERYTHROPHAGOCYTOSIS

Erythrophagocytosis is a phenomenon in which erythrocytes are phagocytized by the macrophages leukocytes or histiocytes in the peripheral blood although no single or fixed mechanism can be considered to be operative in producing this condition However the primary stimulus seems to lie in the altered nature of the red cells which provokes the macrophages to exercise their phagocytic function since normal intact erythrocytes are not readily engulfed by leukocytes or histiocytes Under the influence of chemical or bacterial poisons as well as in the presence of intensive antigen antibody reactions the reactive protein constituents of the red cells may become so sensitized as to render them an inviting object for the phagocyte Zinkham and Diamond (19ɔ2) classified the conditions inducing erythrophagocytosis into congenital erythrocyte abnormalities (sickle cell anemia and hemolytic anemia of the newborn) and acquired abnormalities including chemical and bacterial toxins antigen antibody reactions symptomatic diseases and idiopathic disorders Long ago Hektoen (1906) found erythrophagocytosis to occur in vitro when he mixed normal serum with the cells separated from the blood of individuals belonging to A B or AB group Although this thermostabile serum factor was considered to be a special type of antibody producing erythrophagocytosis called hemopsonin it was later demonstrated to be nothing but anti A or anti B agglutinin Apt (1931) reported the occurrence of mononuclear erythrophagocytosis in the blood of a newborn infant which may be explained on the basis of the accelerated hemolysis frequently witnessed during the neonatal period Zinkham and Diamond (19ɔ2) were able to demonstrate this phenomenon in slide preparations made from the white cell layer obtained by centrifugation of the blood of a patient with idiopathic hemolytic anemia The blood sample was collected with the addition of a small amount of anticoagulant left standing at room temperature for 30 minutes and the white cell layer was incubated for 2 hours at 37 C before inspection Under the microscope the erythrocytes are seen to collect around the granulocytes and monocytes which slowly engulf the red cells by projecting numerous pseudopods Once phagocytized into the cytoplasm of the macrophage the color of hemoglobin gradually fades and the red cell is transformed into a ghost

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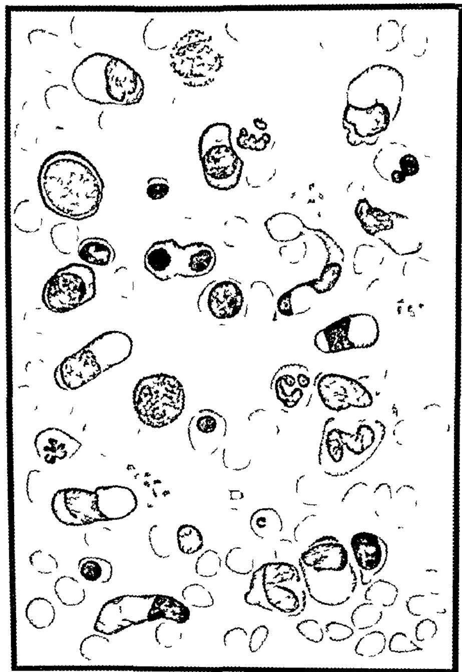
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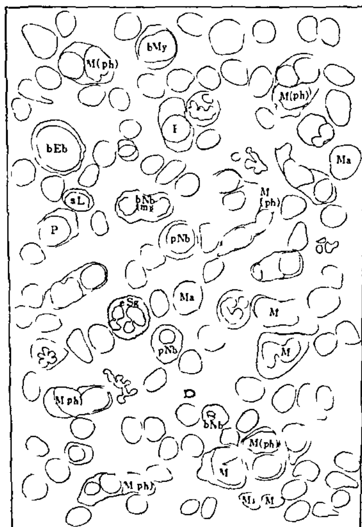
PLATE 83

Erythrophagocytosis

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Plate 83 Erythrophagocytosis





bMy	Basophilic myelocyte
P	Plasmacyte
Mi	Microcyte
Ma	Macrocyte
bNb	Basophilic normoblast
pNb	Polychromatophilic normoblast
eSg	Eosinophilic segmentocyte
M	Monocyte
M(ph)	Monocyte with erythrophagocytosis
sL	Small lymphocyte
(m)	Mitotic figure

Plate 83 depicts erythrophagocytosis in anemia (Courtesy of Dr T C Wyatt)

46 NUCLEOPHAGOCYTOSIS

Nucleophagocytosis refers to a phenomenon characterized primarily by the presence of an increased number of macrophages in the circulating blood which have ingested the nuclei of disrupted cells under some pathologic influences When the phagocytized nucleus maintains a relatively intact chromatin pattern the macrophages are sometimes called tart cells which must be distinguished from L E cells described elsewhere The chromatin of the ingested nucleus often appears to be somewhat condensed occasionally vacuolated and a dark stained thick rim is formed near the periphery With the lapse of time however these phagocytized nuclei being subjected to the enzymatic influence of the macrophage cytoplasm undergo gradual disintegration and fragmentation as evidenced finally by the presence of intracytoplasmic debris Since normal leukocytes are not usually ingested by the macrophages the condition initiating nucleophagocytosis must involve some alteration on the part of the leukocytes which arouse or activate the phagocytic function of the macrophage Most frequently such changes are likely to occur in the polymorphonuclear neutrophils which have ingested foreign bodies circulating in the blood stream such as fat droplets and bacteria In diseases accompanied by bacteremia and septicemia the microorganisms invading the blood stream are usually engulfed by the microphages which in turn are phagocytized by the macrophages mobilized from the reticuloendothelial system

In subacute bacterial endocarditis the phenomenon of nucleophagocytosis has been frequently observed This disease usually caused by *Streptococcus viridans* or *Str hemolyticus* is characterized by the development of hemorrhagic foci of embolic nature in the capillaries and complicated by visceral infarcts One may observe on smear preparations of either peripheral or venous blood the presence of numerous macrophages containing variable amounts of bacteria nuclear debris or even apparently intact neutrophils ingested in their cytoplasm Occasionally erythrophagocytosis may also be seen in such preparations In this disease accompanied by moderate anemia and leukocytosis the most peculiar symptom consists of the appearance of petechiae and of slightly nodular and definitely tender spots (Osler s nodes) often occurring in crops Whether or not the appearance of these signs is in any way related to the tidal variation in the occurrence of nucleophagocytosis is not clear

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46 NUCLEOPHAGOCYTOSIS

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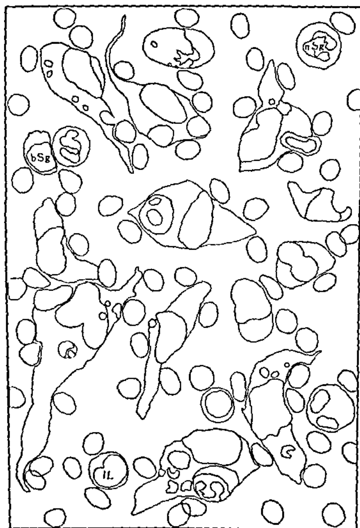
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PLATE 84

Nucleophagocytosis

(Subacute Bacterial Endocarditis)



nSg Neutrophilic segmentocyte
bSg Basophilic segmentocyte
lL Large lymphocyte

Plate 84 is a peripheral blood smear made from capillary blood (ear lobe puncture) of a 45 year old patient wiht chronic mitral regurgitation and endocarditis Numerous reticuloendothelial cells are seen to have engulfed into their cytoplasm a variety of foreign substances such as erythrocytes leukocytes and other debris all of which are in various stages of intracellular disintegration (Courtesy of the Mayo Clinic)

Plate 84 Nucleophagocytosis (Subacute Bacterial Endocarditis)



47 L.E. CELL AND L.E. PHENOMENON

The L E (lupus erythematosus) cell discovered by Hargraves in 1948[1] is usually a granulocyte occasionally a monocyte which has phagocytized a large homogeneous or amorphous inclusion body probably of nuclear origin This phenomenon is said to occur in the presence of a component of gamma globulin called L E factor which attacks the blood leukocytes and eventually dissolves their nuclei by depolymerizing desoxyribonucleic acid (Haserick et al 1950) Frequently the free amorphous nuclear material is surrounded by a collar of phagocytizing leukocytes and a rosette is thus formed The process of producing the L E cells and the consequent formation of rosettes under the influence of the L E factor is known as the L E phenomenon

Demonstration of the L E phenomenon is a useful means of confirming the diagnosis of certain diseases classified under collagenosis particularly of systemic lupus erythematosus in which this test is said to be specific This biochemical test requires a source of the L E factor nucleoprotein and phagocytic cells all reacting with each other at an optimal temperature A simple technic for performing the test is first to collect and allow the blood to clot by leaving the sample at room temperature for 2 hours The clot is then forced through a screen of fine mesh and the resulting fluid is placed in one or two hematocrit tubes for centrifugation at high speed for about 5 minutes After discarding the serum the buffy coat is used for making smear which are stained by the routine method Under oil immersion magnification the L E cells can be recognized by the presence of nuclear masses phagocytized by neutrophilic granulocytes occasionally eosinophils and monocytes stained bluish purple or reddish brown with granular hazy or homogeneous appearance

The L E phenomenon must be distinguished from the pseudo-L E phenomenon Kurnick (1957) has pointed out that in the pseudo L E phenomenon the inclusions in the cells are mostly intact nuclei and no droplets or extra cellular depolymerized DNA masses are seen Leukoagglutination may occasionally present a picture resembling rosettes in the pseudo-L E phenomenon The distinction between nucleophagocytosis and L E phenomenon has been emphasized by Hargraves (1954) who stated that the tart cell has no relation to the L E phenomenon despite the view entertained by some observers that the tart cell is a precursor of the L E cell

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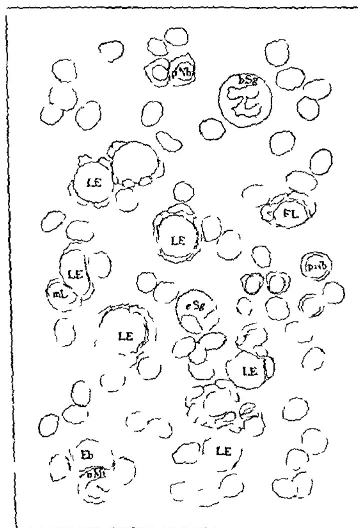
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PLATE 85

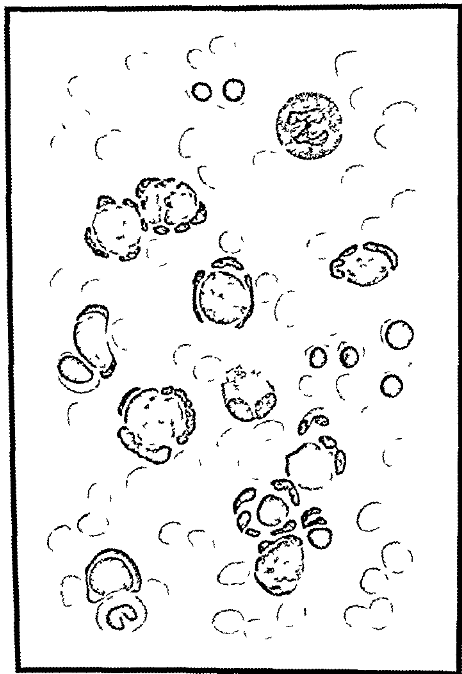
Lupus Erythematosus (L E) Cells



LE	L E cell
pNb	Polychromatophilic normoblast
bSg	Basophilic segmentocyte
eSg	Eosinophilic segmentocyte
nMt	Neutrophilic metamyelocyte
mL	Mesolymphocyte

Plate 85 depicts typical lupus erythematosus (L E) cells (Courtesy of Dr G P Hennigar)

Plate 85 Lupus Erythematosus (L E) Cells



48 GAUCHER'S DISEASE

Gaucher s disease is a rare chronic familial disease of lipid metabolism clinically characterized by progressive splenomegaly skin pigmentation pinguecula formation on the sclera and usually by the extensive involvement of the bones throughout the body Histopathologically the involved tissue reveals the presence of numerous lipoid laden macrophages known as Gaucher cells varying greatly in size according to the amount of foreign material ingested in the cytoplasm This disease was first described by Gaucher in 1882 as a type of primitive epithelioma of the spleen without leukemia and the nature of the lipid concerned was found to be a cerebroside which was later identified as kerasine by Epstein (1924) and by Lieb (1924) The etiologic trait appears *to be hereditary and transmitted as a simple dominant due to a mutation* although it is also likely to be due to the action of an autosomal recessive gene which in the homozygous states causes an intracellular metabolic defect

The gradually but continuously enlarging spleen is the earliest and the most outstanding sign of the disease the organ attaining dimensions greater than *in any other known condition In young infants certain neurologic manifesta*tions including neck rigidity convergent strabismus and opisthotonus may develop Rarely hepatomegaly and lymphadenopathy may be encountered while arrested physical and mental development is usual The formation of wedge shaped pinguecula on the sclera and light yellowish brown discoloration of the conjunctiva on either side of the cornea are characteristic The most remarkable and extensive changes occurring in practically all bones are due to the accumulation of Gaucher cells in the marrow spaces producing the so-called Erlenmeyer flask deformity at the ends of long bones The scattered areas of rarefaction and condensation give rise to a mottled appearance of the bone on x ray films

The typical Gaucher cell is a large macrophage with one or several nuclei and provided with a cytoplasm containing numerous light blue stained wavy fibrils Each of these fibrils as described by DeMarsh and Kautz (1957) is bounded by a single dense membrane and contains a homogeneous matrix in which are embedded tubule like subunits representing the molecular kerasine or lipoprotein units This substance sometimes called Gaucher lipoprotein is chemically composed of lignoceric acid sphingosine and d galactose or glucose and a water soluble glycolipid probably a polycerebroside has also been isolated from the Gaucher tissue

Hematologically anemia leukopenia and thrombocytopenia are usually found either singly or in combination in varying degrees However there is little evidence in favor of accelerated blood cell regeneration or of increased cell destruction Detection of Gaucher cells in the materials obtained by splenic or sternal puncture decides the diagnosis

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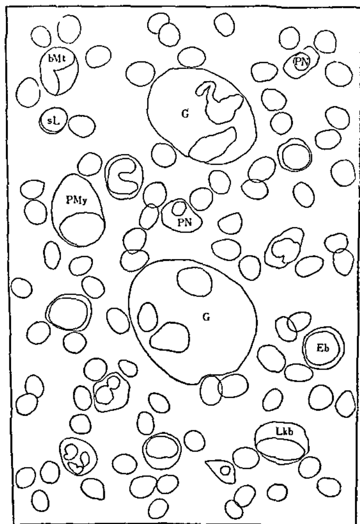
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PLATE 86

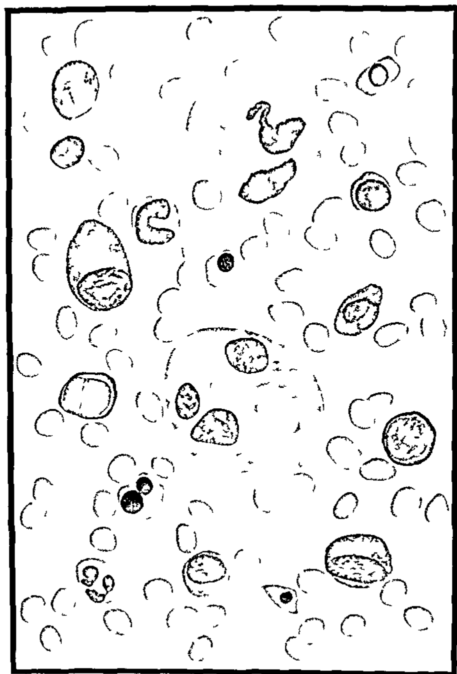
Gaucher's Disease
(Sternal Myelogram)

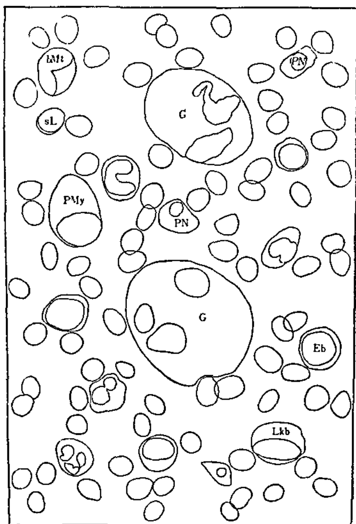


G Gaucher cell
bMt Basophilic metamyelocyte
PMy Promyelocyte
PN Polychromatophilic normoblast
Eb Erythroblast
Lkb Leukoblast

Plate 86 shows the sternal marrow picture in Gaucher's disease

Plate 86 Gaucher s Disease (Sternal Myelogram)





G	Gaucher cell
bMt	Basophilic metamyelocyte
PMy	Promyelocyte
PN	Polychromatophilic normoblast
Eb	Erythroblast
Lkb	Leukoblast

Plate 86 shows the sternal marrow picture in Gaucher's disease

Plate 86 Gaucher's Disease (Sternal Myelogram)

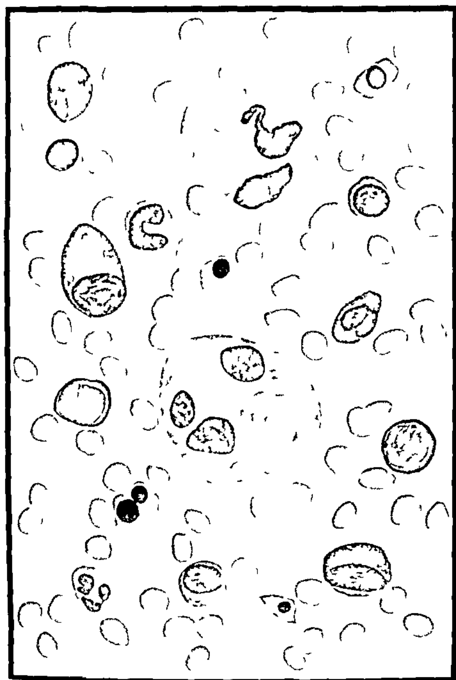
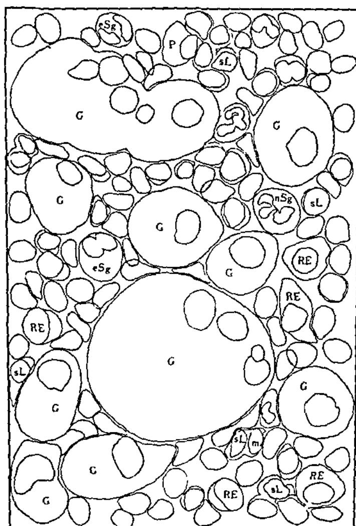


PLATE 87

Gaucher's Disease
(Splenogram)

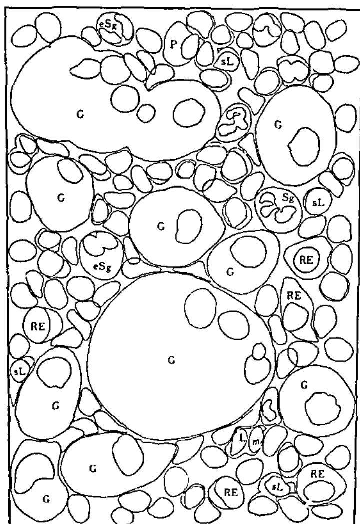


G Gaucher cell
RE Reticuloendothelial cell
nSg Neutrophilic segmentocyte
eSg Eosinophilic segmentocyte
P Plasmacyte

Plate 87 is the splenogram in Gaucher's disease (Courtesy of Dr W Dameshek)

Plate 87 Gaucher's Disease (Splenogram)





G	Gaucher cell
RE	Reticuloendothelial cell
nSg	Neutrophilic segmentocyte
eSg	Eosinophilic segmentocyte
P	Plasmacyte

Plate 87 is the splenogram in Gaucher's disease *(Courtesy of Dr W Dameshek)*

49 NIEMANN PICK'S DISEASE

Niemann Pick s disease is like Gaucher s disease a manifestation of con genitally disturbed lipid metabolism seen almost exclusively in infants and young children clinically characterized by digestive disorders emaciation increasing enlargement of the abdomen due to splenohepatomegaly and fatal termination The involvement of the liver may occur rather early followed by that of the spleen Bone changes so characteristic of Gaucher s disease have not been described in this disease The first report of this condition was made by Niemann (1914) as a new disease which was later classified by Pick (1922) as a type of xanthomatosis The term lipoid histiocytosis (Bloom) has been suggested as a synonym for this disease Adult lipoidosis reported by Terry and co-authors (1954) resembles Niemann Pick s disease but the identity of these two conditions is somewhat uncertain

The occurrence of lipid laden cells called Niemann Pick cells in the organs of the reticuloendothelial system characterizes the pathology of this disease These cells result from excessive ingestion of a phosphatide either lecithin or sphingomyelin by the macrophages and vary in size and shape being filled with small round hyaline droplets in the cytoplasm and giving rise to the name foam cells These droplet materials stainable by ordinary fat stains often crowd out the nucleus so as to greatly reduce its size and to make it hyperchromic and pyknotic When the central nervous system is extensively affected the histologic picture resembles that seen in amaurotic familial idiocy (Tay Sachs disease)

The blood shows moderate anemia and leukopenia with relative lymphocytosis and monocytosis The lymphocytes as well as the monocytes of the periphera blood often reveal the presence of one or many vacuoles in the cytoplasm probably resulting from the phagocytosis of plasma phosphatide The blood cholesterol level may be elevated but no bilirubinemia has been observed Positive diagnosis can be made by demonstrating the typical Niemann Pick cells in the materials aspiratd from the bone marrow or spleen

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Chargaff E A study of the spleen in a case of Niemann Pick disease J Biol Chem

49 NIEMANN PICK'S DISEASE

Niemann Pick s disease is like Gaucher s disease a manifestation of con genitally disturbed lipid metabolism seen almost exclusively in infants and young children clinically characterized by digestive disorders emaciation increasing enlargement of the abdomen due to splenohepatomegaly and fatal termination The involvement of the liver may occur rather early followed by that of the spleen Bone changes so characteristic of Gaucher s disease have not been described in this disease The first report of this condition was made by Niemann (1914) as a new disease which was later classified by Pick (1922) as a type of xanthomatosis The term lipoid histiocytosis (Bloom) has been suggested as a synonym for this disease Adult lipoidosis reported by Terry and co authors (1954) resembles Niemann Pick s disease but the identity of these two conditions is somewhat uncertain

The occurrence of lipid laden cells called Niemann Pick cells in the organs of the reticuloendothelial system characterizes the pathology of this disease These cells result from excessive ingestion of a phosphatide either lecithin or sphingomyelin by the macrophages and vary in size and shape being filled with small round hyaline droplets in the cytoplasm and giving rise to the name foam cells These droplet materials stainable by ordinary fat stains often crowd out the nucleus so as to greatly reduce its size and to make it hyperchromic and pyknotic When the central nervous system is extensively affected the histologic picture resembles that seen in amaurotic familial idiocy (Tay Sachs disease)

The blood shows moderate anemia and leukopenia with relative lymphocytosis and monocytosis The lymphocytes as well as the monocytes of the peripheral blood often reveal the presence of one or many vacuoles in the cytoplasm probably resulting from the phagocytosis of plasma phosphatide The blood cholesterol level may be elevated but no bilirubinemia has been observed Positive diagnosis can be made by demonstrating the typical Niemann Pick cells in the materials aspiratd from the bone marrow or spleen

PEFEI ENCES

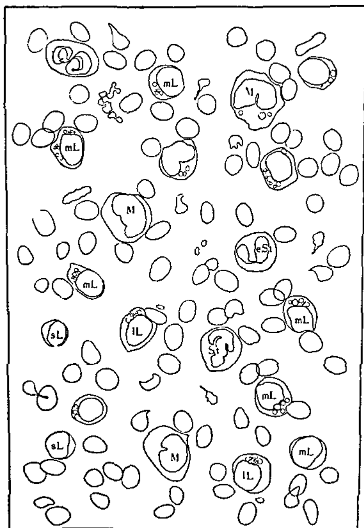
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PLATE 88

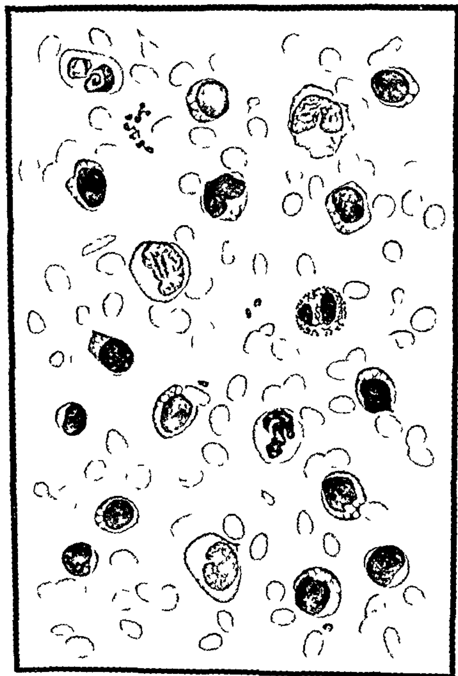
Niemann Pick's Disease
(Peripheral Blood)

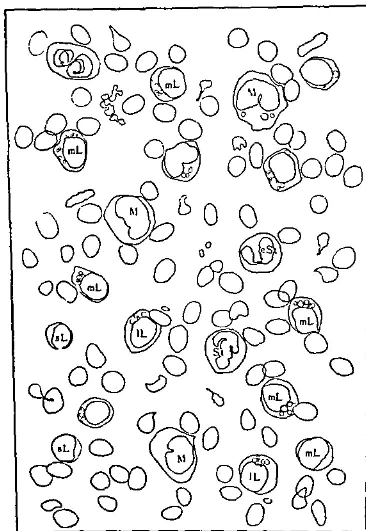


lL	Large lymphocyte
mL	Mesolymphocyte
sL	Small lymphocyte
M	Monocyte
nSt	Neutrophilic stab cell
eSg	Eosinophilic segmentocyte

Plate 88 is the peripheral blood picture of an 18 month old infant suffering from Niemann Pick's disease in which the most striking finding is the presence of numerous fat particles in the cytoplasm of many lymphocytes and a few monocytes. Anisocytosis and poikilocytosis of red cells are notable changes associated with marked hypochromic anemia.

Plate 88 Niemann Pick's Disease (Peripheral Blood)





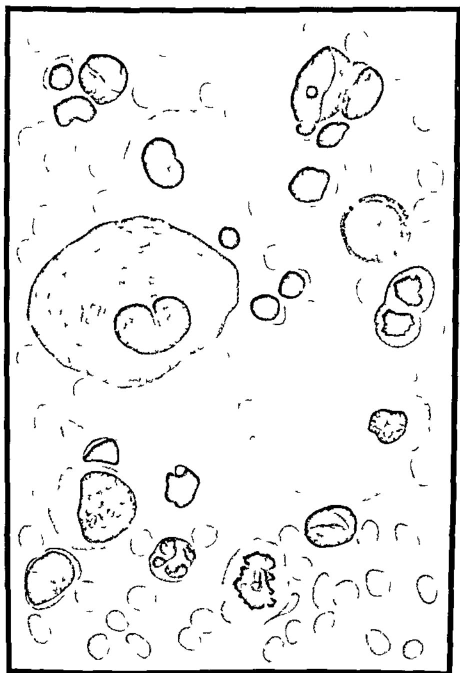
lL Large lymphocyte
mL Mesolymphocyte
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PLATE 89

Niemann-Pick's Disease
(Sternal Myelogram)

Plate 89 Niemann Pick's Disease (Sternal Myelogram)



N P Niemann Pick cell
PMk Promegakaryocyte
Lkb Leukoblast
PMy Promyelocyte
nMy Neutrophilic myelocyte
PEb Proerythroblast
(m) Mitotic figure

Plate 89 is the sternal marrow picture which is characterized by the presence of many Niemann Pick cells loaded with lipid matter as indicated by the abundance of vacuoles in the cytoplasm These cells can be differentiated from the promegakaryocyte the cytoplasm of which contains typical azurophilic granules instead of vacuoles

50 NEUROBLASTOMA AND NEUROBLASTEMIA

Neuroblastoma synonymously known as sympathicoblastoma sympathogonioma or sympathoblastoma is a neoplastic disease in which the embryonic formative cells in the adrenal medulla undergo malignant proliferative changes and metastasize into various organs and tissues Sympathoblasts or sympathogonia (Poll) represent a group of undifferentiated pluripotential cells derived from the embryonic ganglion crest which migrate into the visceral areas to form the anlage of the sympathetic nervous system finally differentiating into unipolar and multipolar neuroblasts These cells may lie dormant in the adrenal medulla for varying lengths of time or may at any time undergo proliferative changes Although medullary origin of the tumor is most common the ubiquitous occurrence of the e cells throughout the body accounts for the multiplicity of its location Pobertson (191o) classified the tumors according to their structural differences into sympathoblastoma ganglioneuroblastoma ganglioparaganglioneuroblastoma and ganglioglioneuroblastoma The tumors have been differentiated into those with metastases chiefly to the liver (Pepper type) and those characterized by the tendency to metastasize into the cranial bones (Hutchison type) although almost all cases represent a mixed type

The early symptoms of this disease are usually unnoticed and the first attention is attracted to the protrusion of the eyeball with a reddish blue discoloration of the eye lids There may be a few enlarged lymph nodes of the neck which distort the facial appearance of the patient The liver may gradually gain in size but splenomegaly is seldom een Upon x ray examination the cranial bones show a tendency for granularity in the compacta while increased trabecullations are noted in the long bones

Hematologically aside from the development of extremely severe anemia the leukocytes are either normal or slightly increased in number of which as much as 25 per cent may consist of immatur myeloid cells including myelocytes and even myeloblasts Nucleated red cells are also found in small numbers but thrombocytopenia may be alarming The bone marrow tends to show a generalized decrease in the myeloid elements with a relative abundance of erythrogenic cells The most striking feature of bone marrow histology as described for the first time by Kato and Wachter (1938) is the presence of a number of large primitive cells in pseudorosette formation or in syncytial masses These cells are provided with small amounts of cytoplasm while the relatively large nuclei exhibit a granular chromatin pattern covered by scattered coarse granules The nucleoli are not clearly discernible and the cell boundaries are indistinct A moderate number of these cells are seen to be in mitosis A case reported by Okinaka and his associates (1956) was most unique in that neuroblasts were found in the peripheral blood to the extent of 46 5 per cent of the total 5 000 leukocytes increasing to nearly 100 per cent just prior to death The condition was designated as neuroblastemia by the authors

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PLATE 90

Sympathicoblastoma
(Sternal Myelogram)

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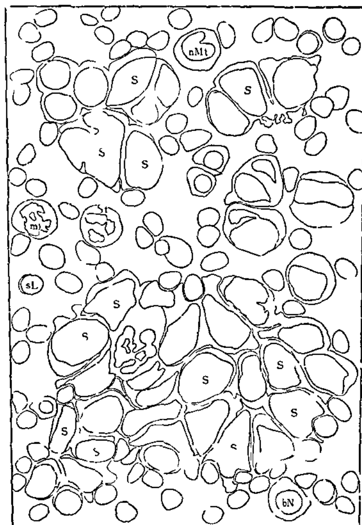
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PLATE 90

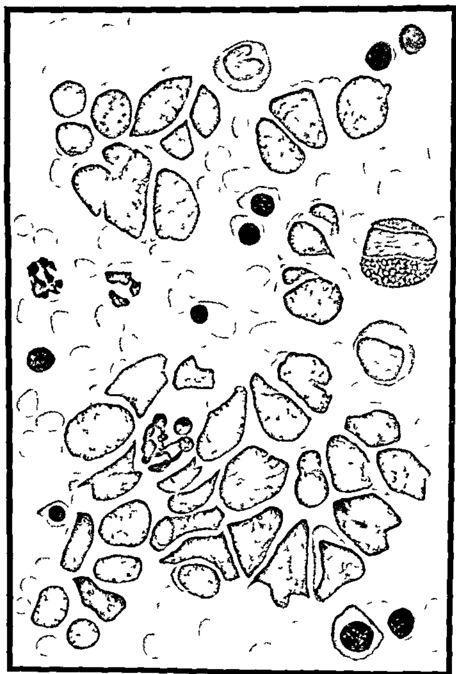
Sympathicoblastoma
(Sternal Myelogram)

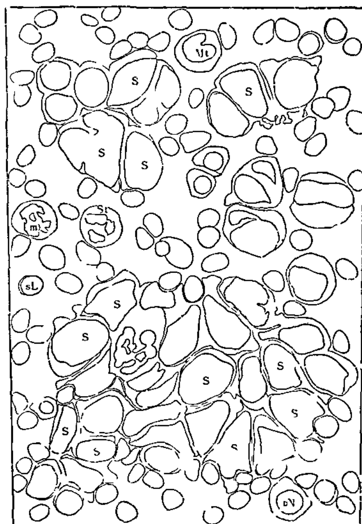


S Sympathoblast
nMt Neutrophilic metamyelocyte
nSt Neutrophilic stab cell
bN Basophilic normoblast

Plate 90 is the picture seen in the sternal marrow fluid aspirated from a 2 5 years old male child demonstrating the presence of numerous sympathicoblasts metastasizing from the primary focus in the adrenal medulla This was the first instance of adrenal sympathicoblastoma with metastases in the cranial orbital vertebral and other bones (Hutchison type) in which the diagnosis was established by sternal marrow puncture observed and reported by K Kato and H E Wachter

Plate 90 Sympathicoblastoma (Sternal Myelogram)





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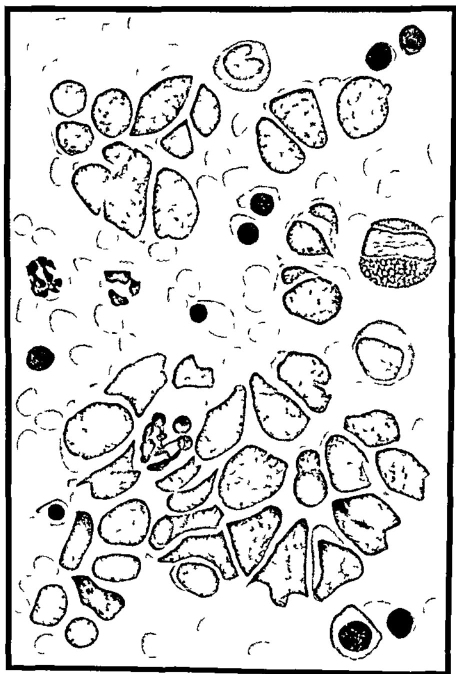
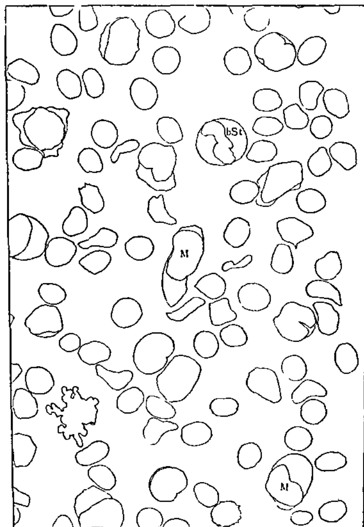


PLATE 91

Neuroblastoma
(Peripheral Blood)



M Monocyte
bSt Basophilic stab cell

Plate 91 is the peripheral blood picture of a 29 years old male patient neuroblastoma associated with a leukemoid neuroblastemia The malignant blast cells are characterized by the scanty and fluid appearing cytoplasm sc nucleus is almost barren These cells showed a tendency t disseminate wide y into the bone marrow and produced a remarkable neuroblastemia during t terminal stage (Courtesy of Drs S Okinaka K Nakao K Kinugasa F Takal and K Ohtsuki)

Plate 91 Neuroblastoma (Peripheral Blood)

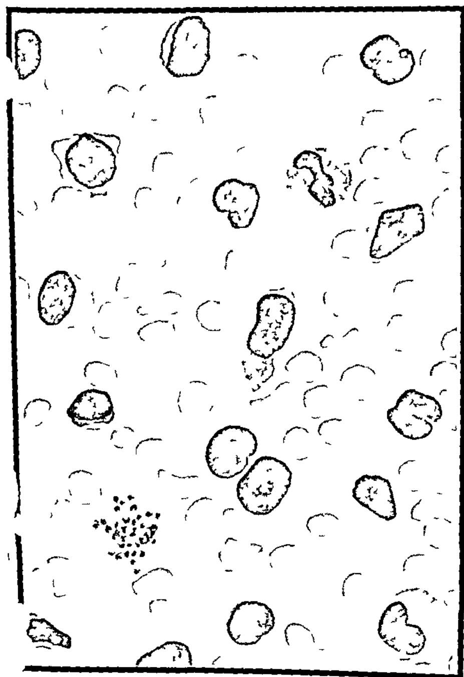
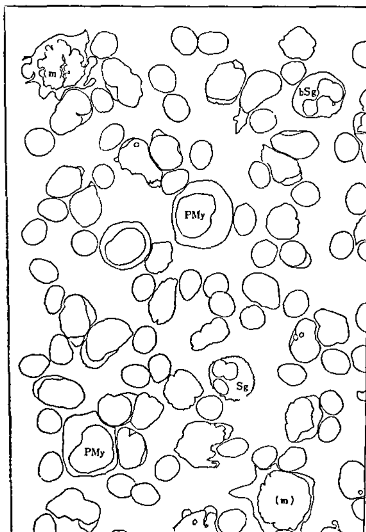


PLATE 92

Neuroblastoma
(Myelogram)



PMy Promyelocyte
eSg Eosinophilic segmentocyte
bSg Basophilic segmentocyte
(m) Mitotic figure

Plate 92 is the sternal marrow picture of the patient with neuroblas n accompanied by a neuroblastemia described in the preceding plate The pro liferating cells (not indicated by any abbreviation letters) are morpholog i identical with those seen in the peripheral blood

Plate 92 Neuroblastoma (Myelogram)



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